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- ОПРЕДЕЛЕНИЕ ПОРОГА «ГОТОВНОСТИ ПЛАТИТЬ» ПРИ ОДОБРЕНИИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ В УСЛОВИЯХ РОССИЙСКОГО ЗДРАВООХРАНЕНИЯ, РАССЧИТАННОГО НА ОСНОВЕ ПАРИТЕТА ПОКУПАТЕЛЬНОЙ СПОСОБНОСТИ
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BUDGET IMPACT OF USING RECOMBINANT COAGULATION FACTOR VIII IN PATIENTS WITH HEMOPHILIA A

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Abstract: *The market entry of modern recombinant blood coagulation factors VIII have brought the quality and safety of medical help for hemophilia A patients to a higher level. Before 2015 only full-length recombinant blood coagulation factor VIII (INN octocog alfa) was available to patients within the framework of the federal reimbursement program "7 Nosologies", while in 2015 the first B-domain deleted recombinant factor VIII (INN moroctocog alpha) was included in the program for the first time and also became available to patients. During the analysis of clinical and economic characteristics of these drugs it was found that the cost of treatment with full-length factor VIII is lower than with B-domain deleted factor VIII due to lower risk of inhibitor development and clinically-proven reduction in bleeding frequency on prophylaxis in full-length recombinant factor VIII, as well as to higher consumption of B-domain deleted factors for effective bleeding prophylaxis. As a consequence, clinically unreasonable patient switching from full-length to B-domain deleted factors requires "7 Nosologies" budget increase comparing to 2014.*

Key words: *hemophilia A; "7 nosologies" program; recombinant blood-clotting factors; full-length recombinant factor VIII; B-domain deleted recombinant factor VIII; budget impact; direct costs.*

Hemophilia A is a severe genetic disorder characterized by defect of blood clotting due to reduction or absence of synthesis of coagulation factor VIII (FVIII) [1]. The lack or deficiency of FVIII causes prolonged bleeding occurring as a result of surgical procedures as well as minor trauma or spontaneously. The most common bleedings are located in joints (hemarthroses) and muscle, resulting in degenerative changes that decreas the patients' quality of life and working ability, as well as located in brain and other vital organs, which increases the risk of fatality [2].

According to the World Health Organization (WHO), the incidence of hemophilia A is 5 to 10 cases per 100,000 male births [3]. Hemophilia accounts for up to 95% of all genetic clotting disorders in the Russian Federation requiring therapy, with hemophilia A (ICD 10: D66.0) occurring more often than hemophilia B and accounted for 80-85% of the total number of hemophilia cases [4]. To date, 6,793 patients with hemophilia are registered in Russia, 5,801 of them have hemophilia A [4].

Severe form of hemophilia with factor level lower than 1% is identified in early childhood and characterized by posttraumatic and spontaneous bleedings into joints, muscle, and internal organs, the incidence of which may be up to 20 or 30 per year. This form of hemophilia is the most common (about 70% of all cases) and most often results in disability when therapy is insufficient.

The research has shown that moderate form of hemophilia (factor level of 1-5%) occurs in 4% of the cases and is characterized by moderate hemorrhagic syndrome with bleeds into joints and muscle. This condition is diagnosed in adolescence or later.

In mild hemophilia that occurs in less than 30% of cases, FVIII level exceeds 5% and the clinical course is marked by infrequent and less intense posttraumatic or postoperative bleedings [1, 2].

Currently the only therapeutic approach to the treatment of patients with hemophilia A is the lifelong hemostatic replacement therapy with plasma-derived or recombinant blood clotting factors VIII (level A evidence) belonging with "Blood coagulation factors" group (ATC code B02BD) that are represented in the Russian Federation by 4 international nonproprietary names (INN) and more than 15 brand names (BN) [2]. These drugs are prescribed in on-demand and prophylaxis regimens for adult and pediatric patients, depending on the course of the disease [1, 5].

One of the most severe complications of replacement therapy in patients with hemophilia A is the development of FVIII inhibitors, which makes the FVIII treatment ineffective. Inhibitor hemophilia A is characterized by prolonged uncontrollable bleeding episodes (including life-threatening) resulting from absolutely ineffective treatment with factor concentrates. The approaches to the treatment of inhibitor patients are considerably different and result in significant increase of treatment costs [6].

According to the Bonn Protocol, patients with high-titer inhibitors are treated with high doses of FVIIII (immune tolerance induction therapy, ITI) and, after successful completion of the course of treatment, patients return to FVIII replacement therapy. Only bypassing agents are used for reversal and prevention of bleedings in inhibitor patients. To date, bypassing agents currently available in the Russian pharmaceutical market include anti-inhibitor coagulant complex (AICC) and eptacog alpha [activated] [5].

As the onset of the disease often occurs in childhood, the total lifetime treatment cost per patient determines considerable economic impact. At the same time, lifelong clotting factor replacement therapy is the only available therapeutic approach by the moment, while the early onset of treatment together with the implementation of prophylactic treatment model enables the patients to sustain a normal lifestyle with life expectancy approaching that of the healthy population.

Considering the above, the problem of selection of medical technologies for treatment of hemophilia A in modern healthcare must be considered from the point of view of clinical and economical effectiveness.

Initially, for the treatment of hemophilia A patients only plasma-derived clotting factors VIII (pdFVIII) obtained from donor plasma were used and it was only the early 2000s when the first recombinant factors VIII (rFVIII) appeared in the international pharmaceutical market. The advantage of using of rFVIII is their greater safety due to the absence of donor plasma components. To date, both pdFVIII and rFVIII presented by octocog alfa have been available to patients within the framework of "7 Nosologies" program. In 2014 the program was revised and moroctocog alfa was added to the list of reimbursed rFVIII for hemophilia A treatment. The inclusion of the new molecule in this federal program dictated the need in pharmacoeconomic assessment.

Pharmacoeconomic budget impact model of use of rFVIII used for the presented analysis was developed in 2013 and approved by the National Institute for Health and Care Excellence (NICE), UK. This model has been successfully used internationally and may be used for evaluating of cost-effectiveness of reimbursement programs for patients with hemophilia A.

The study was conducted in accordance with the data on hemophilia A patient population, and efficacy, safety and costs of the prescribed therapies.

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The main sources of data concerning patient population and therapy efficacy and safety were the published national clinical studies and other official sources of information. In the absence of national data, international data was used with particular emphasis on meta-analysis and systematic literature reviews.

One-year treatment costs for patents with hemophilia A under prophylaxis and on-demand regimens using full-length recombinant factor VIII (FL-rFVIII, INN octocog alfa) and B-domain deleted recombinant factor (BDD-rFVIII, INN moroctocog alfa) were estimated, taking into account their efficacy, bleeding rates under both regimens, and the probability of inhibitor formation. Based on the estimates of one-year treatment costs, budget impact was analyzed, in accordance with patient population treated with recombinant factors in the Russian Federation.

The structure of the model shown in Fig.1 implies the existence of pediatric and adult populations treated with rFVIII under on-demand and prophylaxis regimens. This treatment is administered throughout the entire analyzed year and is only terminated in case of development of coagulation factor inhibitors. In such cases, patients are switched to ITI until inhibitor elimination or until ITI therapy is deemed ineffective. In case of successful inhibitor elimination, patients are transferred back to rFVIII prophylaxis regimen, and in case of a failure, to bypassing agent therapy under on-demand or prophylaxis regimens.

In the course of this study, efficacy and safety used for further cost estimation were expressed as bleeding rates under on-demand or prophylaxis regimens, and as probability of inhibitor development.

Estimated costs of one-year therapy with FL-rFVIII and BDD-rFVIII were directly used for further analysis of budget impact while the final costs of ITI and bypassing agent therapies were adjusted to take into account the probability of inhibitor development and the need in bypassing therapy.

In the course of cost analysis, the following costs to be the base of budget impact analysis were estimated:

1. On-demand and prophylaxis therapy with FL-rFVIII and BDD-rFVIII;
2. ITI therapy; and
3. Bypassing therapy using eptacog alpha and AICC.

The resulting budget impact analysis data were extrapolated to the entire population of hemophilia A patients receiving rFVIII, and allowed to evaluate the economic impact of transferring patients from one technology to another.

Efficacy and safety analysis conducted as a part of this study allowed to identify and formulate a number of differences between the analyzed drugs from the standpoint of pharmacokinetics, consumption and immunogenicity. The results are shown in Fig.2.

From the standpoint of pharmacokinetics that directly affects clinical properties of the drug, the following distinctions were identified:

- The published meta-analysis reported the average elimination half-life for FL-rFVIII is 14.3 hours and for BDD-rFVIII - 11.3 hours [13]; and
- This translates to 2.53 times greater BDD-FVIII necessary to maintain FVIII concentration of 1IU/dL using a 3-day per week (72 hour) dosing schedule compared to FL-FVIII [14].

The following main differences in immunogenicity were identified:

- The systematic literature review and meta-analysis indicated that the probability of inhibitor development per year during therapy with BDD-rFVIII and FL-rFVIII equals 0.019 and 0.010, respectively, in previously treated patients [15];
- This indicator per month equals 0.001597 and 0.000837 and for BDD-rFVIII and FL-rFVIII, respectively.
- Identified difference in immunogenicity is not statistically significant [15].

Also these drugs have been considered in terms of the particular application represented by the following distinctions:

- Prophylaxis using BDD-rFVIII is associated with higher consumption of the drug compared to FL-rFVIII [13], and
- Higher risk of inhibitor development during treatment with BDD-rFVIII that requires additional ITI and bypassing therapy.

Efficacy indicators included in the comparative analysis were bleeding frequency in patients treated with on-demand or prophylaxis regimens, while safety indicators were probability of inhibitor development for each of technologies. Efficacy and safety criteria as well as the data sources are shown in Table 1.

The literature review has revealed that compared technologies do not differ in bleeding frequency when used on-demand. When prophylaxis regiment was used, however, bleed rates differ, with 0.55 episodes per month for FL-rFVIII and 1.4 episodes per month for BDD-rFVIII (based on 6.6 and 16.8 episodes per year, respectively) [13].

Table 1. **Efficacy and safety indicators used in this study**

Indicator	Full-length recombinant factor VIII	B-domain deleted recombinant factor VIII	Source	Evidence level
Bleeding frequency per month (on demand treatment)	2.7	2.7	Annual bleeding frequency estimated as 32.3*	
Bleeding frequency per month (prophylaxis)	0.55	1.4	Gruppo RA et al. [13]	IA
Probability of inhibitor development in previously untreated patients (per month)	0.007934	0.007934	Iorio A et al. [16]	IA
Probability of inhibitor development in previously treated patients (per month)	0.000837	0.001597	Xi M et al. [15]	IA

*The mean number of bleeds per patient with severe hemophilia A, calculated based on the results of 4 major studies (Miners AH et al., 1998; Schramm W et al., 2002; Tagliaferri A et al., 2008; and Valentino LA, 2012), was about 32.3 episodes per year.

At the same time, it is noteworthy that meta-analysis conducted by Gruppo RA et al. showed that prophylaxis with BDD-rFVIII over the course of one year increases factor consumption by 36% compared to FL-rFVIII, which also has an impact on the entire treatment budget for patients with hemophilia A [13].

Parameters of patient population and prescription of drugs under different treatment regimens used in this analysis are shown in Table 2. The first column shows parameters and the second shows their basic numerical expression.

Table 2. **. Parameters of patient population and prescribed treatments used in cost analysis (based on the federal statistics and RF Ministry of Health's open data, as well as on the data provided by experts)**

Parameter	Basic indicator
Patient population parameters	
Adult patients, %	50.0
Pediatric patients (children and adolescents), %	50.0
Previously untreated patients, %	5.7
Previously treated patients, %	94.3
Weight of adult patient, kg	70.0
Weight of previously treated pediatric patient, kg	35.0
Weight of previously untreated pediatric patient, kg	14.0
FVIII prescription parameters	
Adult patients, on-demand treatment, %	59.0
Adult patients, prophylaxis, %	41.0
Pediatric patients (children and adolescents), on-demand treatment, %	30.0
Pediatric patients (children and adolescents), prophylaxis, %	70.0
Treatment with bypassing agents	
Eptacog alfa, %	50
Anti-inhibitor coagulant complex, %	50

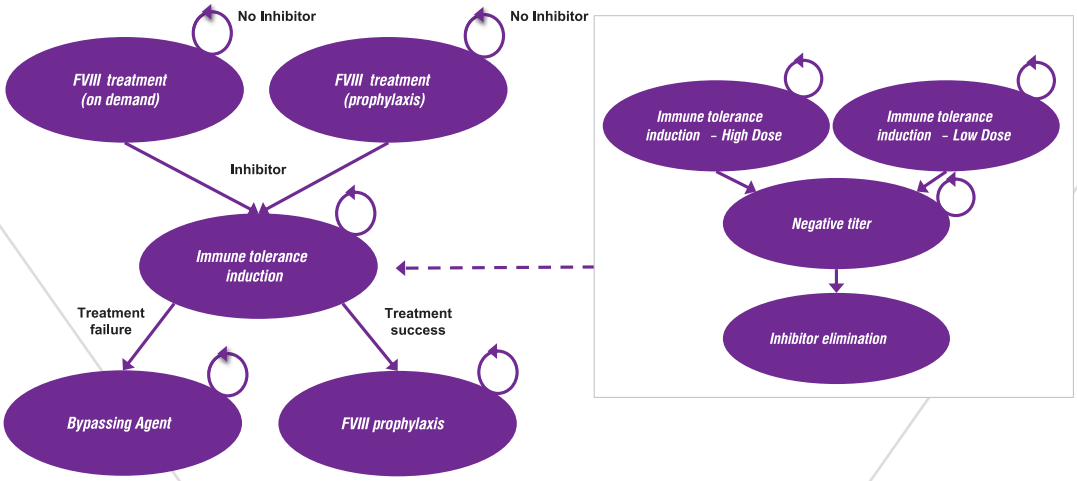

Figure 1. Structure of budget impact model of treatment for patients with rFVIII in patients with hemophilia A.

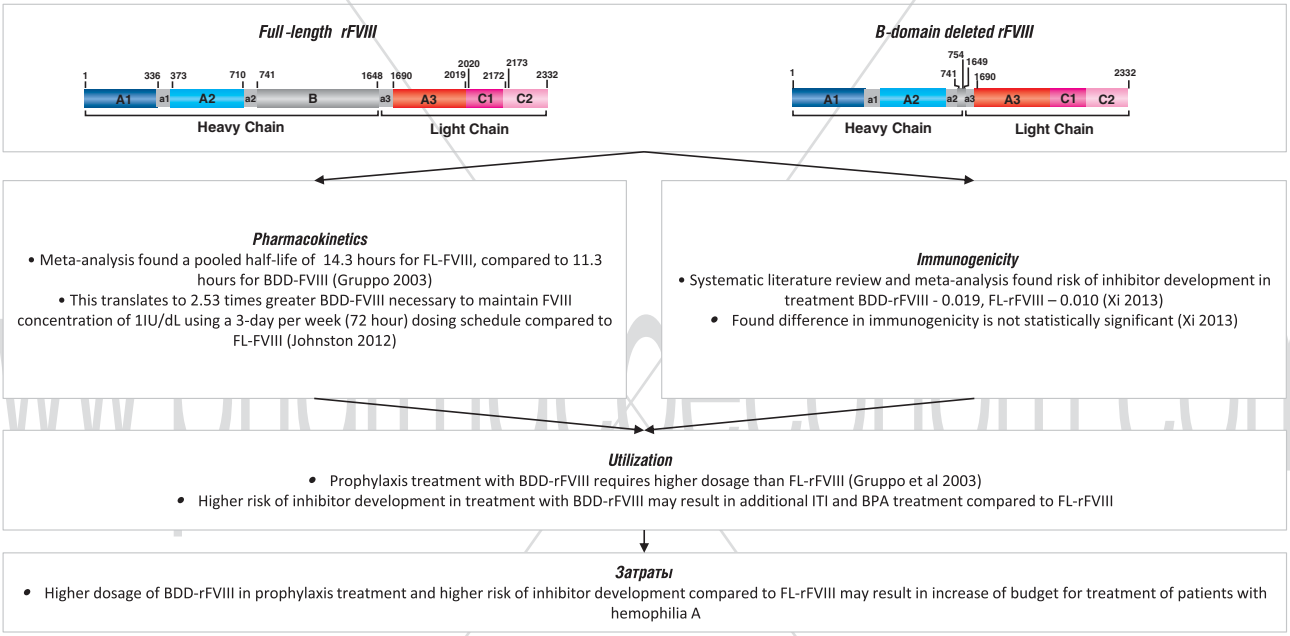

Figure 2. Results of analysis of efficacy and safety of FL-rFVIII and BDD-rFVIII.

All of the listed above parameters were used in cost analysis and enabled to evaluate the mean total costs of patient management using FL-rFVIII and BDD-rFVIII, with the local specifics taken into account.

The average dosages of the drugs in accordance with the official indications were used in the cost analysis of the monthly and annual costs of therapy for hemophilia A patients, as shown in Table 3.

According to the instructions for use of octocog alfa (Advate®, Recombinate®, Kogenate® FS) and moroctocog alfa (Octofactor®, ReFacto AF®), dosages needed to stop one bleed are comparable for all of these drugs and are calculated based on the following: mild bleeding: 20-40 IU/kg; hemarthrosis: 30-60 IU/kg. Therefore 30 IU/kg was assumed to be the mean value regardless of the product.

The necessity of dosage increase of BDD-rFVIII used in prophylaxis compared to FL-rFVIII was based on the data of Gruppo RA et al. meta-analysis [13].

The above-mentioned efficacy and safety parameters were used to estimate total costs of therapy and for further evaluation of budget impact. The resulting mean costs of treatment per one average patient per year are shown in Table 4.

Table 3. **Dosages used in the study**

Treatment regimen	Dosage
On-demand	
FL-rFVIII on-demand, IU/kg	30
BDD-rFVIII on-demand, IU/kg	30
FL-rFVIII on-demand, number of infusions per bleed	1.25
BDD-rFVIII on-demand, number of infusions per bleed	1.25
FL-rFVIII on-demand, number of bleeds per month	2.7
BDD-rFVIII on-demand, number of bleeds per month	2.7
Prophylaxis	
FL-rFVIII prophylaxis, consumption (IU/kg/month)	260
BDD-rFVIII prophylaxis, dosage increase, % [14]	36.0%
BDD-rFVIII prophylaxis, consumption (IU/kg/month)	354
FL-rFVIII prophylaxis, number of bleeds per month [14]	0.55
BDD-rFVIII prophylaxis, number of bleeds per month	1.4

Table 4. **Costs of treatment using recombinant preparations per one average patient per year, rubles.**

Preparation	Full-length recombinant factor VIII	B-domain deleted recombinant factor VIII
Price per IU*	11.86 руб.	11.27 руб.
Recombinant factor VIII cost	1 369 357 руб.	1 723 650 руб.
ITI cost	213 594 руб.	393 188 руб.
Bypassing agents cost	0 руб.**	0 руб.**
TOTAL	1 582 951 руб.	2 116 838 руб.

* The final price of the 2015 federal tender VAT excluded was used in the analysis. The calculation was based on 1,000 IU dosage as the most common dosage in the Russian Federation.
** At the 1-year horizon, ITI therapy in a population of 1,200 patients will be effective in 100% cases.

To estimate the impact of switching patients from one recombinant drug to another on the budget of healthcare system, there were two scenarios modeled:

- "7 Nosologies" program budget with 100% of patients receiving only FL-rFVIII; and
- "7 nosologies" program budget with BDD-rFVII included in the program and a number of patients switched to this new therapy.

The population of patients receiving therapy with recombinant factors comprised about 1200 patients about 600 (50%) of whom were children and adolescents.

The results of budget impact analysis are shown in Fig.3.

With the tender price of FL-rFVIII (11.86 rubles per IU), total costs of treatment per year for the modeled patient population, taking into account the patient distribution by types of therapy, as well as of efficacy and safety of prophylaxis with FL-rFVIII was estimated as about 1 billion 900 million rubles. Modeled budget adjusted to 50% of patients' switching to B-domain deleted products (tender price - 11.27 rubles per IU), the modeled budget, in turn, will exceed the current budget (under which 100% of patients receive full-length factors) by 17%, constituting in total 2 billion 220 million rubles. Transition of 100% patients will require additional costs amounting to 640.6 million rubles (34% increase).

Therefore considering the history of 2014 final tender prices, treatment of patients with hemophilia A with octocog alfa within the framework of "7 Nosologies" is cost effective and will ensure the optimum spending of budget funds.

CONCLUSIONS

1. The total cost of treatment of one patient with FL-rFVIII (INN octocog alfa) with the tender price per unit of 11.86 rubles amounts to 1,582,951 rubles per year while, when BDD-rFVIII (INN moroctocog alfa) is used with tender price per unit of 11.27 rubles, it amounts to 2,116,838 per year.
2. This difference in the costs of therapy results from lower probability of inhibitor development and clinically proven reduction in bleed frequency on prophylaxis using full-length factor VIII as well as from higher consumption of B-domain deleted rFVIII needed for effective prophylactic treatment.
3. Modeling the budget for a population of 1,200 patients receiving only FL- rFVIII with the tender price mentioned above results in the total costs of 1 billion 900 million rubles.
4. The budget for the same patient population with 50% of patients switched to BDD- rFVIII will need to be increased by 17% to amount of 2 billion 220 million rubles.
5. In turn, transition of 100% of patients to BDD-rFVIII will require costs increase by 34% (640.6 million rubles increment) compared to the budget needed to treat 100% patients with FL-rFVIII.

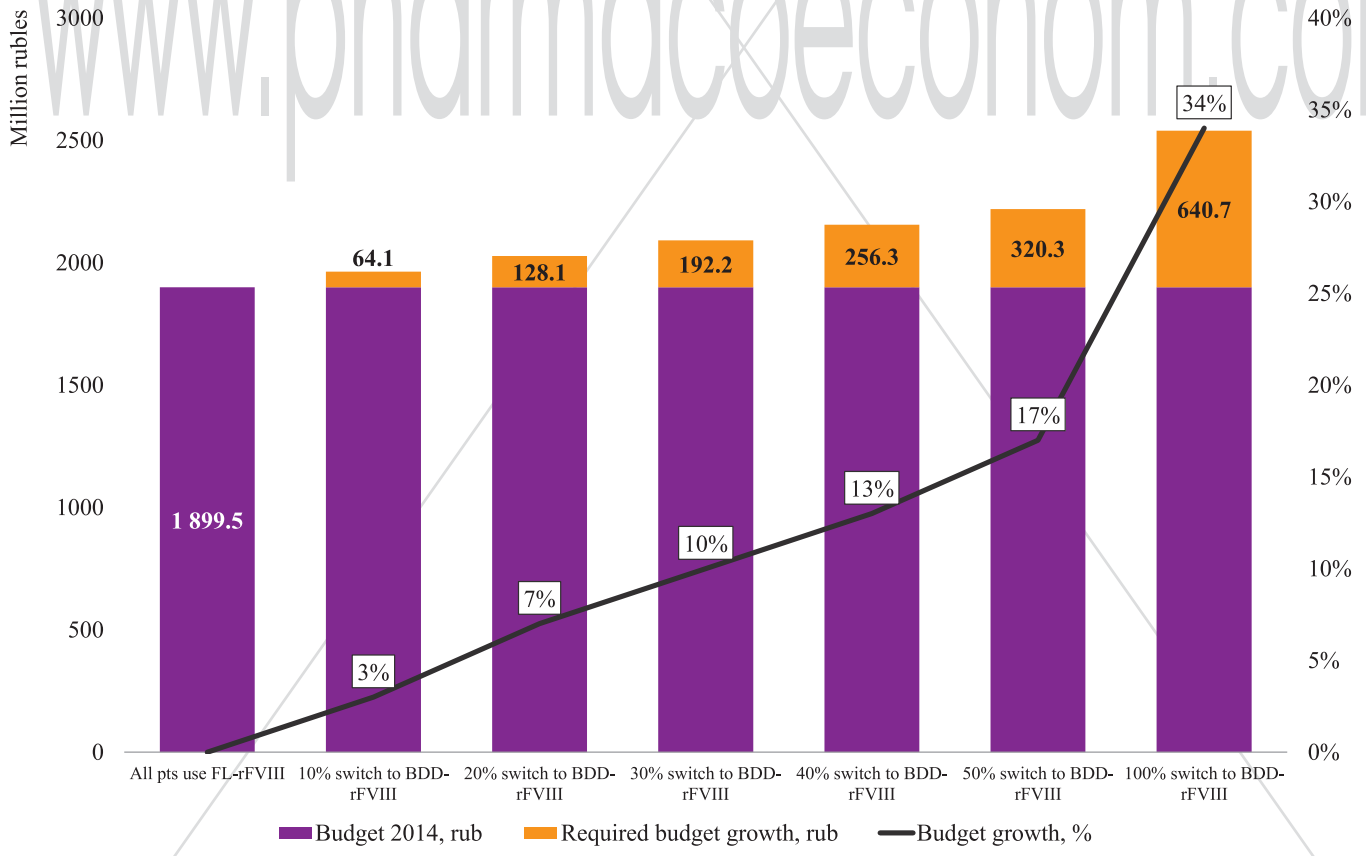

Figure 3. Results of budget impact analysis taking into account current consumption of FL-rFVIII (100%) and switching a number of patients to BDD-rFVIII included in "7 Nosologies" program in 2014.

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