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- АНАЛИЗ ФАРМАКОЭКОНОМИЧЕСКИХ И КЛИНИКО-ЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ, ОПУБЛИКОВАННЫХ НА БАЗЕ НАУЧНОЙ ЭЛЕКТРОННОЙ БИБЛИОТЕКИ «ELIBRARY.RU» (РИНЦ) ЗА ПЕРИОД С 2005 ПО 2015 гг.
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

MARKET REVIEW OF MEDICINES USED IN THE TREATMENT OF HEMOPHILIA UNDER THE FEDERAL PROGRAM "7 NOSOLOGIES"

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Summary: *Hemophilia is one of the rare, socially significant, hereditary diseases drug supply of which centralized in the framework of the program "7 nosologies" at the expense of the Federal budget. According to IMS Health, in 2015 the consumption of medicinal drugs used in the treatment of hemophilia reached 11.2 billion RUB that shows an increase of 16.9% compared to 2010. The main drivers of market growth have become the primarily raising awareness of the disease and the increase in diagnosis led to growth of the patient population as a whole, as well as understanding of the need for effective and quality care that led to a rise of the prescription of the preventive therapy, in which a comparably larger consumption of the medicines for the patient leads to a significant improvement in outcomes and safety of patients. The improving of the quality of medical care is also implemented through the inclusion into the program of modern recombinant medicines, possessing the best safety profile in comparison to the medicines obtained from the plasma of donated blood. Every year the budgetary allocation for the treatment of high-cost nosology in general and for hemophilia increases, that indicates the primary focus of health aimed for improving of the quality of life of patients.*

Key words: *hemophilia, 7 nosologies, blood coagulation factors, bypassing medicines, plasma derived medicines, recombinant medicines.*

Hemophilia is a rare hereditary disease resulting from mutation of a gene on the X chromosome, leading to disruption of blood clotting, which in turn leads to the development of traumatic and spontaneous bleeding in soft tissues, joints and internal organs and causes a high level of disability of patients [1,3,9]. Currently, the only therapeutic approach to the management of patients with hemophilia is a lifelong substitutive therapy with high cost blood clotting factor concentrates, which helps to reduce disability in the population of patients and to maintain the level of life quality comparable to a healthy population. Depending on the severity of the disease and its clinical manifestations and the individual characteristics of patients, the therapy can be prescribed in on demand or prophylaxis regimens. In case of on demand therapy the blood clotting factor concentrates are prescribed for the stop of already developed bleeding and during scheduled surgical procedures; in prophylaxis regimen medicines are infused regularly to prevent the development of bleeding, which allows to maintain the level of coagulation factors above 1% and minimizes the development of spontaneous bleeding. It is important to note that regardless to the assigned treatment regimen, the patient requires continuous access to the medicines, that affects the timeliness of medical care and the reduce of the risk of serious complications that causes the urgency of outpatient therapy.

Since 2008 the provision of medicines for patients with hemophilia has been taking place in the framework of the program of the centralized purchase of medicines intended for the treatment of patients with hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, myeloleukemia, multiple sclerosis and also after transplantation of organs and/or tissues (FL On amendments to the Federal law "Of Federal budget for 2007" N 132-FL of July 17, 2007), that is also called "7 Nosologies" [7, 8].

Providing subsidized blood clotting factor concentrates is carried out for groups of patients with the following inherited deficiencies of clotting factors:

– Hemophilia A – deficiency of coagulation factor VIII (FVIII). The prevalence of hemophilia in most countries is 10-14 patients per 100 000 men. According to the open data published by the Ministry of health of the Russian Federation in 2014, the total number of patients with hereditary coagulopathy and consisting on the account in the register of patients with hemophilia, is 8 284 patients, with 70% of them or 5799 patients are accounted for hemophilia A [2].

– Hemophilia B – deficiency of coagulation factor IX (FIX); it accounts 12% of the total number of patients with hemophilia or 994 patients [2].

– Inhibitor hemophilia – a special case of hemophilia A or B, which is one of the most serious complications of substitution therapy in hemophilia and is characterized by the occurrence of an inhibitor to the administered factor that leads to a lack of effectiveness of substitution therapy. It develops among 15-30% of patients with severe disease. This form of the disease is characterized by the development of long non-stop bleeding, including life threatening bleeding, because of the absolute ineffectiveness of therapy with factor concentrates [1,8,11-13].

– Von Willebrand disease – deficiency of von Willebrand factor which is one of the most common deficiencies of coagulation factors. It occurs in 1% of the population and can be diagnosed among men and women [2].

The substitution therapy of hereditary deficiencies of coagulation factors can be implemented by plasma derived or recombinant concentrates of blood clotting factors [10]. When choosing a specific drug for the therapy, the specialists are guided by such aspects as the long-term effectiveness, ability to stop bleeding without the need for additional injections, the safety and biotech purity. Herewith the benefits of recombinant drugs are the safety, the prospect, the absence of donor blood lack problem and the reduction of allergic reactions. However, plasma derived factors are being used longer in international and local practice, the deferred result of which is known, and the cost of therapy is lower.

By 2015 the list of the drugs of the program had contained 18 international nonproprietary names (INN), 4 of which had been intended for the treatment of patients with hemophilia belonged to blood clotting factors and bypassing drugs (octocog alpha, FVIII, FIX and eptacog alfa [activated]) [4]. In 2014 there was the re-review of the restrictive lists of medicines and Section I. of "drugs given to hemophiliacs" list of pharmaceuticals designed to provide individuals with hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, malignant neoplasms of lymphoid, hematopoietic and related tissue, multiple sclerosis, and persons after transplantation of organs/tissues was expanded and increased by 3 additional INNs – moroctocog alpha, antiinhibitor coagulants complex (AICC) and coagulation factor VIII + von Willebrand factor [5]. Thus, currently, under the Federal hemophilia programs provided by the 7 INNs, which comparative characteristics are shown in table 1.

Table 1. Classification of medicinal drugs used in the treatment of different types of inherited deficiencies of coagulation factors.

Hereditary factor deficiency	Plasma derived factors	Recombinant factors
Hemophilia A	FVIII	Octocog alpha Moroctocog alpha
Hemophilia B	FIX	-
Inhibitor Hemophilia A and B	AICC	Eptacog alfa [activated]
Von Willebrand Disease	FVIII + von Willebrand factor	-

According to IMS Health, the total market value of the medicines included in the program "7 nosologies" increased in the period 2010-2015 from 33.5 to 43.8 billion rubles in 2015 (31%). The compound annual growth rate (CAGR) of the consumption of pharmaceuticals in the same period was 6%. (figure 1).

of the market structure of the MP included in the program is provided in figure 2.

Figure 3 illustrates the evolution and the structure of the market of drugs used in the treatment of hemophilia in 2010-2015 in value.

As it is shown in the figure, the market of drugs for hemophilia therapy repeats the main trend of product market of the program "7 nosologies" and is characterized by a sharp decrease in purchases in 2011, followed by stable growth. Overall, in 5 years the market of concentrates of blood clotting factors increased in 27%, slightly below the overall level of growth.

It should be noted that the INN FVIII + von Willebrand factor for the treatment of von Willebrand Disease were in a separate lot in the framework of the Federal tender in 2015, and by the moment they had been included in the lot of total FVIII, so thereby in the period from 2010 to 2014 they could not be isolated from the context of the overall FVIII procurement.

Table 3 shows the consumption of the medicines used in the treatment of different types of inherited deficiencies of coagulation factors, in 2014 and 2015 in monetary terms, and shows CAGR over the last 5 years.

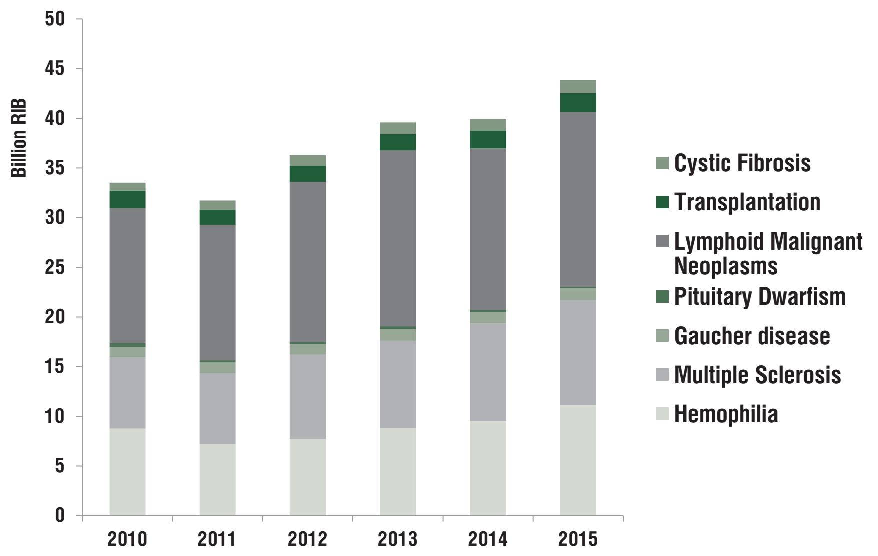

Figure 1. Dynamics of consumption of drugs included in the program "7 nosologies" in monetary terms (2010 – 2015).

According to our analysis, the largest growth in percentage was shown by the market of medicines for patients with cystic fibrosis (the total increase is 58%, CAGR is 10%) and the largest growth in absolute monetary terms was shown by the market of drugs for the treatment of neoplasms of lymphoid, hematopoietic and related tissue. Table 2 shows the consumption of medicines included in the program "7 nosologies", in 2010 and in 2015 in value, as well as the CAGR within the period.

Table 2. The consumption of medicines included in the program "7 nosologies" in 2010 and in 2015 (in value).

Nosology	Year 2010 (billion rubles)	Year 2015 (billion rubles)	CAGR (%)
Hemophilia	8,76	11,16	5,0
Multiple sclerosis	7,16	10,57	8,1
Gaucher Disease	1,06	1,15	1,7
Pituitary dwarfism	0,41	0,14	-19,4
Lymphoid Malignant Neoplasms	13,58	17,63	5,4
Transplantation	1,73	1,89	1,8
Cystic fibrosis	0,82	1,3	9,6
Total	33,53	43,86	5,5

Thus, in general, the most rapidly growing diseases are cystic fibrosis, multiple sclerosis and myeloid leukemia. Hemophilia takes the fourth place and grows at the average level of the whole market of "7 nosologies". The analysis

Table 3. The consumption the medicines used in the treatment of hemophilia (in value).

Hemophilia type	Year 2010 (billion rubles)	Year 2015 (billion rubles)	CAGR (%)
Hemophilia A	6,28	7,15	2,6
Hemophilia B	0,67	1,03	8,8
Von Willerbrand	1,81	2,79	9,1
Disease	-	0,19	-

As it can be seen from the analysis, the drugs for the treatment of hemophilia A occupy a leading place in the total consumption of blood clotting factor concentrates and this fact is primarily associated with the largest subpopulation of patients. Along with this, the drugs for the therapy of an inhibitory form of hemophilia have become the most rapidly growing segment that held 25% of the market hemophilia in 2015.

From 2010 to 2015, the consumption of drugs for the treatment of hemophilia A increased in 14% in value terms and in 40% in volume (international units, IU) (figure 4).

Figure 5 and 6 shows the dynamics of consumption of plasma derived and recombinant FVIII used in the treatment of hemophilia A in volume and value, respectively. From 2010 to 2015 there was an increase of plasma derived FVIII in just 1% in value and in 32% in volume. At the same time, the consumption of recombinant FVIII increased in 77% in value and in 99% in volume. This increase indicates the redistribution of budget

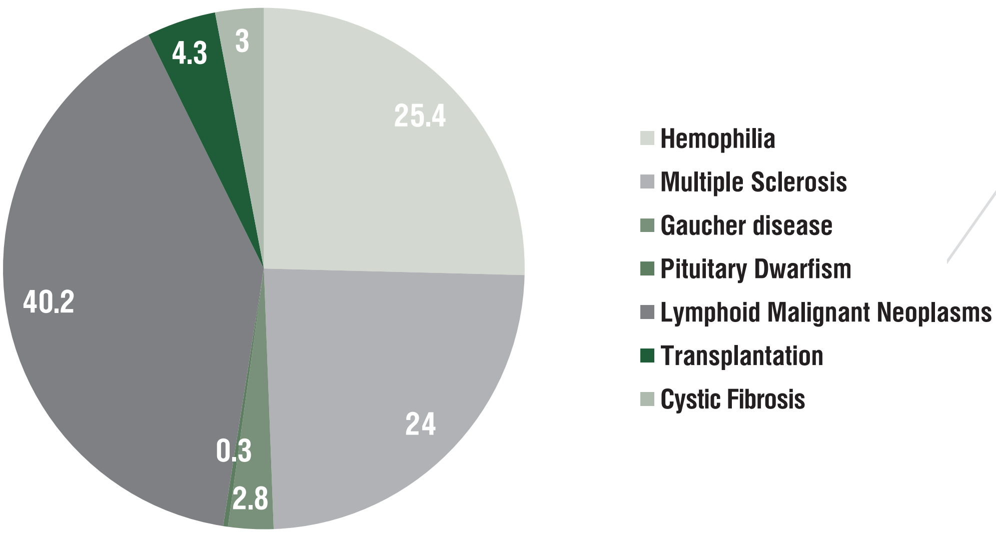

Figure 2. The market structure of the medicines included and purchased in the framework of the program "7 nosologies" in 2015 (in value and percentage).

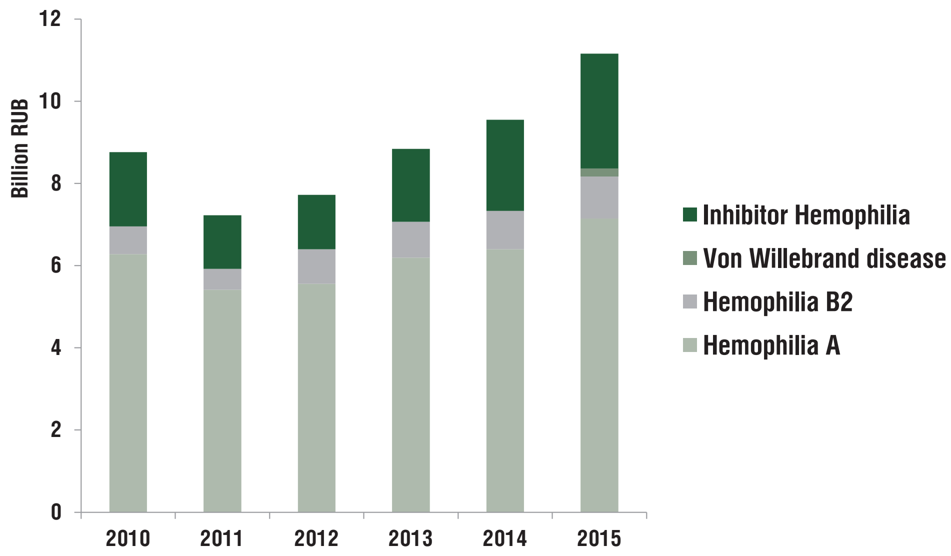

Figure 3. Dynamics of consumption of drugs used in the treatment of hemophilia in value (2010 – 2015).

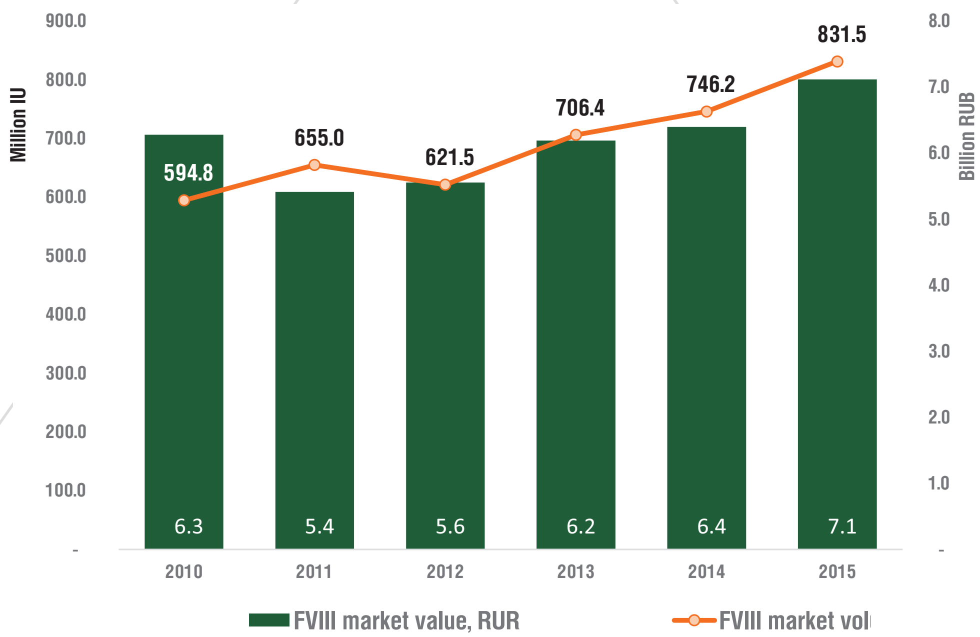

Figure 4. Consumption of drugs used in the treatment of hemophilia A in general, in volume and value (2010 – 2015).

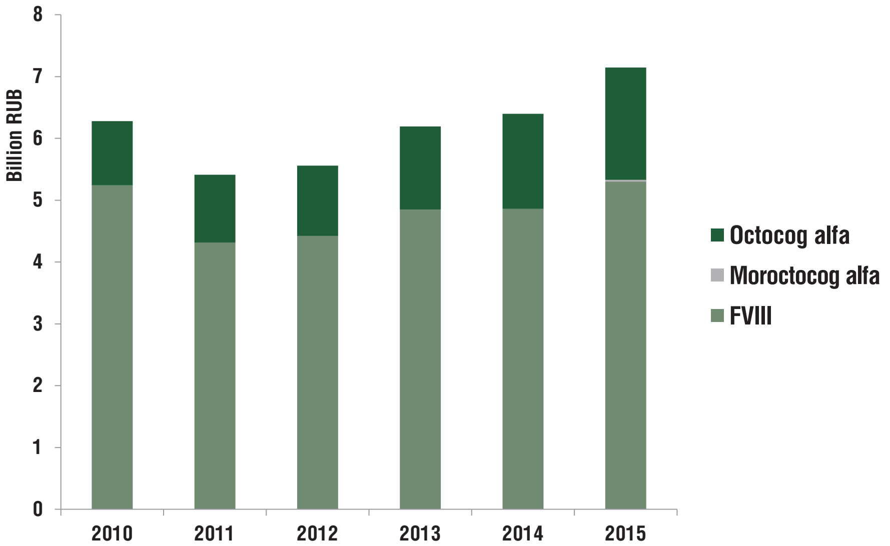

Figure 5. Market dynamics of plasma derived and recombinant FVIII for the treatment of hemophilia A in value (2010 – 2015).

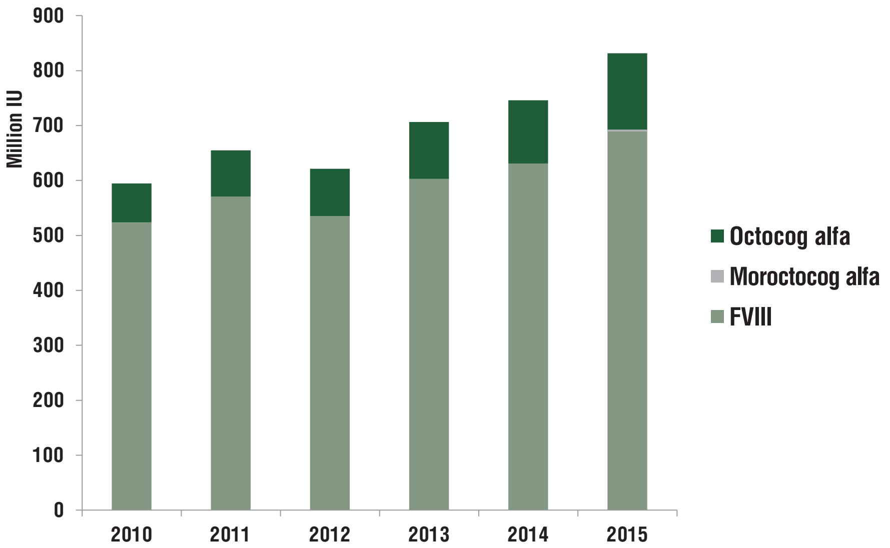

Figure 6. Dynamics of plasma and recombinant drugs for the treatment of hemophilia A market in volume (2010 – 2015).

funds to the direction of advanced technologies that improves the quality of medical care.

On the basis of statistical data the rating of manufacturers of plasma and recombinant drugs for the treatment of hemophilia A in 2010 and 2015 has been also formed (table 4).

Table 4. The rating of manufacturers of drugs used in the treatment of hemophilia A in 2010 and 2015 (in value).

2010		2015	
Manufacturer	Sales, RUB	Manufacturer	Sales, RUB
Octapharma	3 079 149 394	Baxter Int	4 195 135 622
Biotest Pharma	1 101 785 674	Octapharma	1 587 565 260
Baxter Int	1 072 359 979	CSL Behring Gmbh	604 100 953
Bayer Healthcare	550 367 981	Biotest Pharma	293 623 949
CSL Behring Gmbh	476 491 786	Grifols S.A.	237 976 269

As it can be seen from table 4 in 2010 a leading position in sales of FVIII in monetary terms was occupied by the manufacturers of plasma derived products; in 2015 that was the redistribution in favor of the consumption of recombinant products and, accordingly, in favor of manufacturers of these drugs.

A quarter of the market share of consumption among the medicines used for the treatment of patients with hemophilia are bypassing medicines used in the therapy of inhibitor haemophilia. The market of these drugs can be considered only in value, according to the uncoupling of units of the active substance, e.g. the drug AICC can be considered in active units (U) and eptacog Alfa [activated] in mg. From 2010 to 2015 the consumption of drugs for therapy of inhibitor hemophilia in value increased from 1.8 billion to 2.8 billion RUB, that is matched to an increase in 54% (figure 7).

The statistical data about the purchase of AICC was presented only for 2015 in connection with its introduction into the “7 nosologies” program only in 2014. Thus, there is a growing consumption of AICC that can be related to the registered indications for long terms of prophylactic treatment.

Thus, currently there is a stable growth of total consumption of the medicines used in the treatment of hemophilia in general. The pharmaceuticals for the treatment of hemophilia A and inhibitor hemophilia are the main share of the market, which growth of value consumption is attributable by the appearance on the market of innovative products that enhance quality of pharmaceutical care, but at the same time, this requires a higher cost. Also there is a redistribution of funds in the direction of improved technologies, including an increase in the consumption of recombinant products for the treatment of hemophilia A, which are the most secure compared to plasma derived ones.

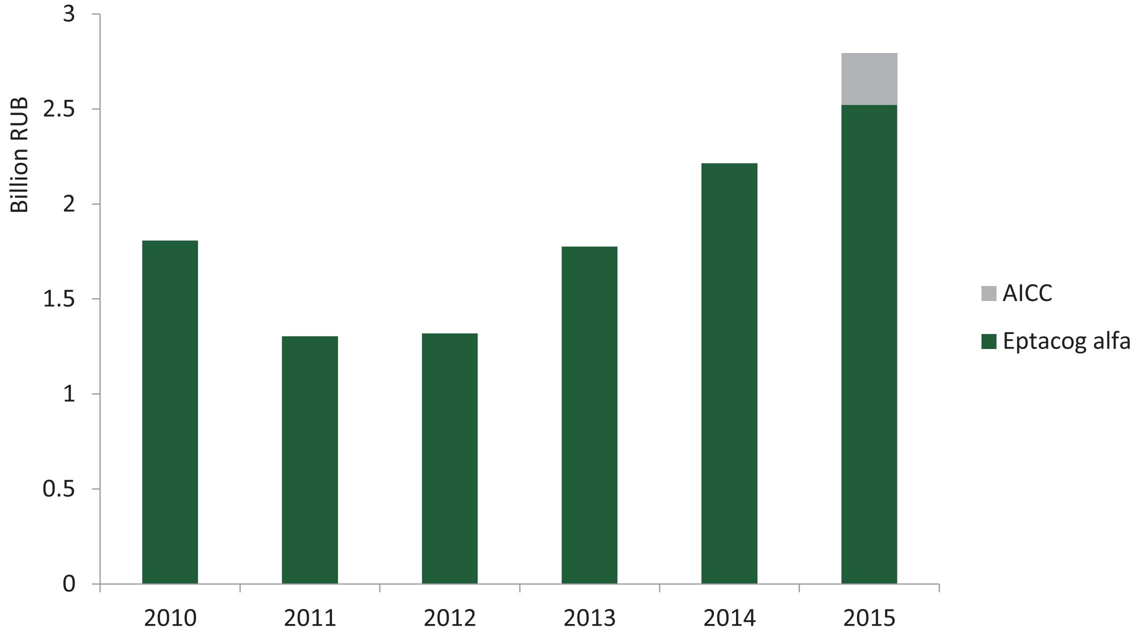

Figure 7. Dynamics of the bypassing drugs for the therapy of inhibitor hemophilia market in monetary terms (2010 – 2015).

It should also be noted that when creating the program "7 nosologies" there was the expiration date defined, which suggested the probability of its transfer from the Federal level to the regional level. However, on 26 April 2016 that was a law N 112-FL "Of amendments of the Federal law "About bases of health protection of citizens of the Russian Federation", which decided the indefinite preservation of the program on the Federal level, which ensures a stable access of patients to expensive life-saving medical care due to the centralization of the procurement and to the preservation of the budget.

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