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- ОПРЕДЕЛЕНИЕ ПОРОГА «ГОТОВНОСТИ ПЛАТИТЬ» ПРИ ОДОБРЕНИИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ В УСЛОВИЯХ РОССИЙСКОГО ЗДРАВООХРАНЕНИЯ, РАССЧИТАННОГО НА ОСНОВЕ ПАРИТЕТА ПОКУПАТЕЛЬНОЙ СПОСОБНОСТИ
- ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ

# PHARMACOECONOMIC ANALYSIS OF IMPLEMENTATION OF CLOTTING FACTOR VIII AND VON WILLEBRAND FACTOR MEDICAL PRODUCTS INTO THE TREATMENT REGIMENS FOR VON WILLEBRAND DISEASE

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**Abstract:** The study established a superior clinical efficacy in bleeding episodes relieving, and the health care resources saving in contrast with the current treatment regimen, when patients with von Willebrand disease Haemate P treatment receive. Thus, Haemate P shows pharmacoeconomic advantage over current treatment regimen of von Willebrand disease, which includes coagulation factor VIII drugs, as well as Wilate pharmacotherapy, as the most effective and cheap treatment scheme.

**Key words:** pharmacoeconomic analysis, von Willebrand disease, clotting factor VIII, von Willebrand factor, vWF, direct costs, indirect costs, budget impact analysis

## Introduction

Von Willebrand disease (vWD) is an inherent blood disease characterized with episodic, spontaneous bleedings, the reason for which is blood clotting disorder due to insufficient activity of von Willebrand factor which assures platelet attachment to the area of affected vessels. Besides, von Willebrand factor is a clotting factor VIII carrier; it stabilizes its structure and delivers to the lesion area.

Profuse and long-term bleedings (nasal, gingival, uterine) as well as muscle and joint hemorrhages are reported in patients with acute deficiency in factor VIII. Besides, long-term bleedings can occur in traumas, teeth extractions and surgeries. Autosomal mode of inheritance conditions similar frequency of von Willebrand disease in patients of both genders. Due to physiological body particularities associated with reproductive function, more common hemorrhagic symptoms are reported in women; approximately 65% of women with vWD suffer from menorrhagia [21].

The treatment of vWD depends on the disease type. According to the current recommendations, plasma products with high content of von Willebrand factor or factor VIII products are used in the treatment of this nosology. Currently there are several factor VIII products on the Russian pharmaceutical market, Octanate, Immunate and Haemoctin are the representatives of this group. These medicinal products contain high concentrations of clotting factor VIII and some amount of von Willebrand factor. At the same time MPs with high concentration specifically lacking von Willebrand factor (Willebrand factor/clotting factor VIII ratio = 1:1 and more) are presented in lesser extent. Thus, taking into consideration wide use of clotting factor VIII MP, in Russia patients with von Willebrand disease cannot receive adequate treatment and higher doses of available MPs are used to achieve hemostatic effect in such patients which leads to additional use of healthcare system resources and risk for complications of the therapy performed (thrombosis).

Considering significant effect of vWD on patient's quality of life, it can be concluded that it affects all life aspects: it affects patient's daily life and communication ability. vWD is a heavy load on the national healthcare system. The costs for individual patient during their life course amount significant

economic losses for the society in general and a life-time, expensive treatment is necessary to fight this disease.

On the basis of the above, it seems reasonable and necessary to determine the most reasonable, from the point of view of pharmacoeconomic analysis, medical technology for the treatment of vWD (comparison of five alternatives - Octanate, Immunate and Haemoctin (clotting factor VIII MPs) and Haemate P and Wilate (clotting factor VIII + Willebrand factor)) by budget impact analysis and costs-efficacy analysis.

## The results of efficacy analysis

The first stage of this pharmacoeconomic analysis was information search of clinical studies devoted to the issue of vWD treatment with clotting factor VIII and von Willebrand factor MPs which revealed a randomized, cross-over, clinical study for evaluation of the possibility to use plasmatic clotting factors concentrates in treatment of patients with severe von Willebrand disease. The study compared four virus-inactivated plasmatic products: Haemate P, von Willebrand factor concentrate containing highly purified von Willebrand factor and two clotting factors VIII containing von Willebrand factor. The effect on the activity of clotting factor VIII, the plasma concentration of Willebrand factor and bleeding episodes relieving were evaluated during the study.

The study results demonstrated that test products have different effects on the bleeding time. The administration of Haemate P resulted in complete or partial correction of bleeding time in 8 out of 10 patients while the concentrate of highly purified von Willebrand factor had no effect on hemostasis. The administration of both clotting factors VIII MPs containing Willebrand factor resulted in the correction of bleeding time only in half (5 out of 10) patients in each reference group. Generally, the administration of Haemate P resulted in a significantly better correction of hemostasis system and bleeding time in comparison with three other products [20].

Other cross-over, clinical study revealed by us was the study performed by S. Lethagen in 1992 [18] in which 5 patients with severe vWD participated. The authors used Duke method for bleeding time determination to evaluate the role of von Willebrand factor contained in five different plasmatic products (three plasmatic concentrates of von Willebrand factor + clotting factor VIII including Haemate P; one MP of plasmatic concentrate of clotting factor VIII containing highly purified von Willebrand factor; one MP containing recombinant clotting factor VIII only) to evaluate the efficacy of the pharmacotherapy performed.

It was determined that the administration of all concentrates except for recombinant clotting factor VIII resulted in the decreased bleeding time except for one patient with poor response to the administration of Haemate P. At the same time, decreased bleeding time preserved longer after the administration of Haemate P (24-36 h) compared to other products.

Thus, on the basis of the data obtained, we concluded that Haemate P is effective and safe medicinal product for relieving of bleeding episodes of



different severity independently on the dosage regimens («on demand» and «prevention»). According to data by PM. Mannucci [20] and S. Lethagen [18], it was established that the administration of Haemate P allows to achieve normalization of hemostasis system parameters 30% more often and completely or partially normalize bleeding time in patients suffering from von Willebrand disease in comparison with other clotting factor VIII MPs containing von Willebrand factor.

**The results of costs analysis**

During cost analysis in this study, the costs for the treatment of patients with vWD were calculated according to the results of the evaluation of real clinical practice of Hematologic scientific center of the MOH of the RF, Moscow (23 patients from 5 regions of the RF) and Republican Center for Hemophilia, Saint-Petersburg (17 patients from 7 regions of the RF). At that average frequency of mild and moderate bleedings, severe and clinically significant bleedings, life-threatening bleedings and the dose of clotting factor VIII MPs used for relieving of bleedings of different severity in three dosage regimens - «on demand», «on demand + short-term prevention» and «prevention» were determined.

Thus, the cost of pharmacotherapy of vWD with clotting factor VIII MPs - Immunate, Octanate and Haemoctin and clotting factor VIII MP + von Willebrand factor - Haemate P and Wilate was evaluated at the first stage of the analysis. The cost of the test medicinal products was determined on the basis of the State Register for Limit Selling Prices [2] or prices for Haemate P and Wilate recommended by the manufacturer as of this study performance. The list of stock keeping units of the test MPs and their cost are presented in Table 1:

On the basis of the data provided in Table 1, the price of the unit of active substance, IU of von Willebrand factor, was calculated. Thus, according to data by Klukowska A. [17] and James G. [16], clotting factor VIII MP Immunate includes von Willebrand factor at concentration of 1/2 of clotting factor VIII, while Octanate and Haemoctin contain von Willebrand factor at a dose comprising 0.3 of the specified concentration of clotting factor VIII. At the same time, the concentration of von Willebrand factor contained in Haemate P is 2.4-fold higher than concentration of clotting factor VIII contained in the pack.

Thus, considering the data on the cost of the test MPs obtained on the basis of the State Register for Limit Selling Prices [2] and prices for Haemate P and Wilate recommended by the manufacturer, average cost of IU of von Willebrand factor was determined for each of the MP and was 29.77 rub., 37.53 rub., 39.72 rub. and 43.15 rub for Immunate, Octanate, Haemoctin, Haemate P and Wilate, respectively (Table 2):

It was determined that in test population of 40 patients, 58% received the treatment in «on demand» regimen, at that, on average 10 bleeding episodes annually are reported in this group, of them: 1.5 episodes of severe and 0.32 episodes of life-threatening bleedings. On average, 17.75 bleeding episodes annually are reported in 14% patients receiving the treatment in «on demand + short-term prevention» regimen, of them: 3.5 episodes of severe and one episode of life-threatening bleeding. On average 3 bleeding episodes annually are reported in the group of patients receiving the treatment in «prevention» regimen (28% patients), at that, only one patient was reported to have an episode of life-threatening bleeding (Figure 1):

We have also evaluated average single doses of clotting factor VIII MPs administered by patients to relieve the bleedings of different severity considering the treatment regimens received («on demand», «on demand + short-term prevention» and «prevention»). The doses used by patients that are presented in Figure 2 are specified calculated as administered amount of clotting factor VIII:

The data presented on Figure 2 demonstrate that average single dose for patients receiving the treatment in «on demand» regimen was 2052 IU for each mild or severe bleeding episode relieving, 2364 IU for severe bleeding episode relieving and 3035 IU for life-threatening bleeding episode relieving. Similarly, single doses administered by patients in «on demand + short-term prevention» regimen were 1900 IU, 2587 IU and 3193 IU in the occurrence of mild or moderate, severe and life-threatening bleeding, respectively, at that, single dose during the prevention period (considering a month course of preventative treatment) was, on average, approximately 1760 IU every 2.5 days. Patients who receive the treatment with clotting factor VIII MPs in «prevention» regimen, on average, used single dose of the MP which was 2667 IU and if profuse bleedings occurred they were relieved by administration of 2722 IU of clotting factor VIII MPs.

Table 1 The cost of stock keeping units of test MP

The stock keeping units of test MP	Cost
Octanate 250 IU	2835 rub.
Octanate 500 IU	5616 rub.
Octanate 1000 IU	11203 rub.
Immunate 250 IU	4101 rub.
Immunate 500 IU	5923 rub.
Immunate 1000 IU	16406 rub.
Haemoctin 250 IU	2967 rub.
Haemoctin 500 IU	5978 rub.
Haemoctin 1000 IU	11925 rub.
Haemate P 250 + 600 IU	16782 rub.
Haemate P 500 + 1200 IU	33564 rub.
Haemate P 1000 + 2400 IU	67128 rub.
Wilate 450 + 400 IU	19539 rub.
Wilate 900 + 800 IU	29956 rub.

Table 2 Evaluation of average cost of IU of von Willebrand factor\*

MP	Immunate			Octanate			Haemoctin			Haemate P			Wilate	
	125 IU	250 IU	500 IU	75 IU	150 IU	300 IU	75 IU	150 IU	300 IU	600 IU	1200 IU	2400 IU	400 IU	800 IU
The content of von Willebrand factor	125 IU	250 IU	500 IU	75 IU	150 IU	300 IU	75 IU	150 IU	300 IU	600 IU	1200 IU	2400 IU	400 IU	800 IU
The price of stock keeping unit	4101 rub.	5923 rub.	16406 rub.	2835 rub.	5616 rub.	11203 rub.	2967 rub.	5978 rub.	11925 rub.	16782 rub.	33564 rub.	67128 rub.	19539 rub.	29956 rub.
Average cost of one IU	29.77 rub.			37.53 rub.			39.72 rub.			27.97 rub.			43.15 rub.	

\* the prices as of the study performance

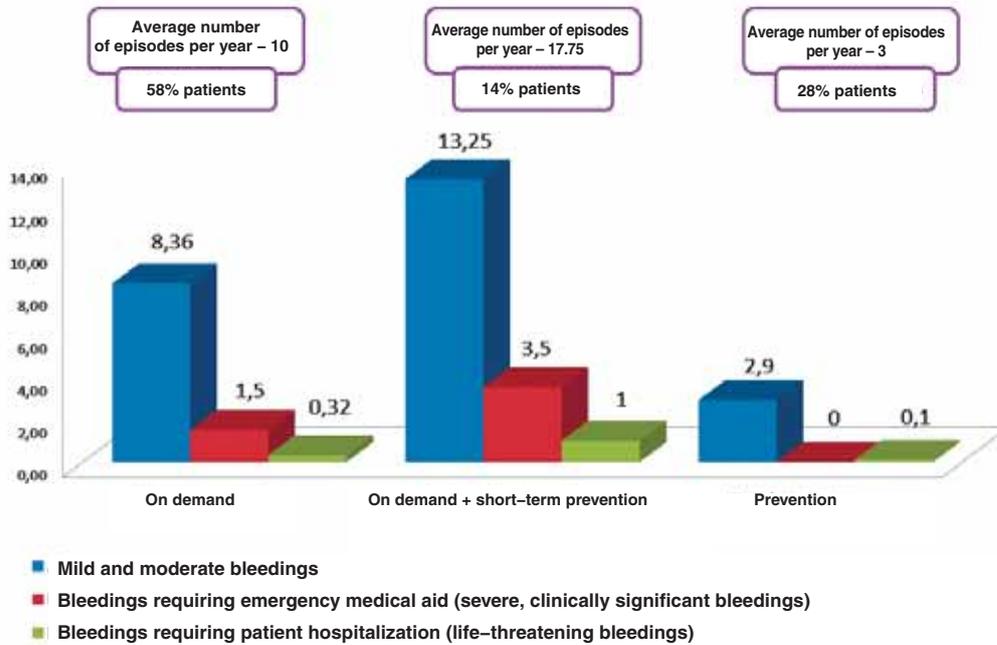


Figure 1. Average number of bleeding episodes depending on the treatment regimen of von Willebrand disease

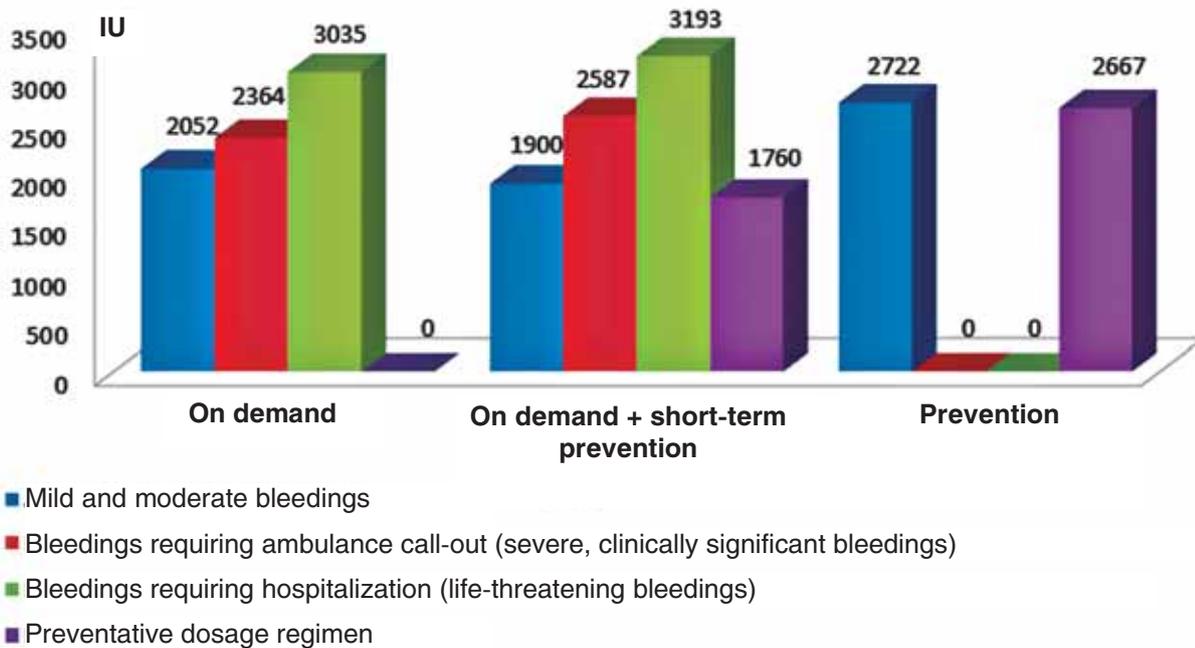


Figure 2. Average single doses of clotting factor VIII

On the basis of data on the concentration of von Willebrand factor in the test MP, the cost of IU of von Willebrand factor, determined as single doses of the MPs in different dosage regimens and in dependence on the bleeding severity, the cost of the treatment of the whole population including 40 patients from Hematological Scientific Center of the MOH of the RF and Republican Center for Hemophilia, Saint-Petersburg, was calculated. While evaluating the treatment cost, it was also considered that the bulk of patients (50%) received the treatment with Immunate, 36% patients received Octanate and 14% received Haemoclin. Annual treatment course cost was calculated for a model of patient weighing 70 kg. At that, the following dosing regimens were considered while analyzing the costs for pharmacotherapy of clotting factor VIII according to practical recommendations for disease treatment:

- In mild and moderate bleedings - single administration of the specified MP dose.

- In severe and clinically significant bleedings - the first administration at a specified dose, afterwards, ½ dose every 24 hours for 4 days.
- In life threatening bleeding - the first administration at a specified dose, afterwards, ½ dose every 12 hours for 3 days, then ½ dose once per 24 hours for 12 days.
- Preventative treatment - 12 injections per month for a year at a specified dose, in case of profuse bleedings - single administration of respective dose of the MP.

On the basis of the data above, taking into consideration the doses of von Willebrand factor received by the patients, the number and severity of bleedings as well as calculated cost of IU of von Willebrand factor for each of the test MP, the cost of bleeding episodes relieving was evaluated depending on their severity. At that, the cost of each type of bleeding episodes relieving



was calculated as the product of necessary dose of von Willebrand factor per patient's body weight (70 kg) and the cost of IU of von Willebrand factor and the number of bleeding episodes (mild or moderate, severe and life-threatening, respectively). Similarly, the costs necessary to relieve bleeding episodes of different severity were calculated when test patient population was switched on Haemate P and Wilate.

Finally it was determined that administration of Haemate P demonstrated lower cost of relieving bleeding episodes of different severity in any dosage regimen due to the lowest cost of IU of von Willebrand factor. Thus, average cost of annual treatment course of each patient who receives clotting factor VIII MPs in «on demand» regimen will be 544,940 rub., while administration of equivalent dose of von Willebrand factor in case of Haemate P will require 437,549 rub. and 674,958 rub in case of Wilate per year. Similarly, average cost of annual treatment course for each patient with von Willebrand disease who receives the treatment in «on demand + short-term prevention» regimen is 1,476,668 rub. while the administration of Haemate P will require 1,170,747 rub. and that of Wilate is 1,805,983 rub. In case of treatment in «prevention» regimen, average cost of annual pharmacotherapy course will be 5,772,112 rub. in current treatment regimen including clotting factor VIII it will be 5,383,621 rub. - in administration of respective doses of von Willebrand factor contained in Haemate P and 8,304,722 rub. per year for Wilate.

The cost saving in the setting of pharmacotherapy with Haemate P which is 107,391 rub in case of treatment in «on demand» regimen, 305,920 rub in «on demand + short-term prevention» and on average 388,491 rub for each patient who receives the treatment in «prevention» regimen is achieved due to the cut in cost of average course dose of von Willebrand factor. On the basis of the above results of evaluation of annual treatment course of von Willebrand disease, it can be concluded that if similar doses of von Willebrand factor are administered, usage of Haemate P in the treatment regimens will allow cost cutting of annual treatment course of each patient on average by 207,533 rub. At the same time administration of Wilate will require additional costs relative to the current treatment regimen on average of 819,549 rub calculated for each patient with vWD and 1,027,082 rub in respect of treatment regimen including Haemate P.

PE analysis «disease cost» including direct and indirect cost evaluation was performed at the next steps of this pharmacoeconomic study after the evaluation of the cost of annual pharmacotherapy course with test MP, at that, the following costs were considered:

- Direct costs included:
  - o Ambulance call-out cost
  - o Hospital treatment cost
  - o Out-patient treatment cost
- Indirect costs included:
  - o The cost of disability of patients with von Willebrand disease
  - o GDP gap associated with von Willebrand disease
  - o Sick pay costs

Cost analysis was performed according to the standards of in-patient medical aid to patients with inherent factor VIII deficiency, inherent factor

IX deficiency approved by the Decree of the MoH of the RF No. 517 dated 6 July 2006 [10] and standard for outpatient aid to patients with inherent factor VIII deficiency, inherent factor IX deficiency, von Willebrand disease approved by the Decree of the MOH of the RF No. 705 dated 14 November 2007 [9]. The prices for diagnostic studies, average cost of one bed day in hospital, surgeries were obtained on the basis of valid price list for fee-based medical services in the Hematological Center of The Main Military Clinical Hospital named after N.N. Burdenko [8] and the Clinical Center of the First Moscow State Medical University named after I.M. Sechenov [7]. The leading assortment positions of the MPs were determined on the basis of IMS data basis as of 2012. The prices for medicinal products were determined on the basis of the State Register for Limit Selling Prices as of 01.05.2013 [2]. This analysis also did not consider the costs for the therapy with clotting factor VIII MPs included in the specified standards.

Finally, on the basis of the data obtained by direct and indirect cost analysis, the costs for the treatment of one patient with von Willebrand disease was determined considering two alternative pharmacotherapy treatment regimens - the current treatment regimen (Immunate, Octanate and Haemoctin) and simulated treatment regimen (Haemate P). The cost rate was evaluated for a model of patient weighing 70 kg considering the study horizon equal to 12 months. The costs obtained during the pharmacoeconomic study and their structure are presented in Table 3:

The data from Table 3 demonstrate that administration of Haemate P will allow cutting the costs for annual treatment course of each patient on average by 210,876 rub. annually due to the decrease in the cost of pharmacotherapy with the MPs, von Willebrand factor, at the same time, the administration of Wilate P will require additional costs at the amount of 836,921 rub relative to the current treatment regimen.

The results of budget impact analysis

Further we performed pharmacoeconomic analysis «budget impact» including the calculation and comparison of the costs for the treatment of vWD in the whole patient population registered in the Russian Federation and receiving the treatment with clotting factor VIII. Thus, according to the data by Andreyeva T.A. [1], currently 3746 patients suffering from vWD are registered in Russia, of them 13% - 496 patients require the treatment with clotting factor VIII and von Willebrand factor (table 4):

Thus, in the current situation characterized by the pharmacotherapy with Immunate (50%), Octanate (36%) and Haemoctin (14%), the necessary budget volume of the healthcare system is approximately 1.194 billion rub. per annual treatment course of the whole patient population with vWD (496 patients). At the same time switching this population on the treatment regimen including Haemate P will require 1.088 billion rub. annually which will cut the costs of the healthcare system budget by 106.4 billion rub or 8.91% of total costs. Saved resources of the healthcare system will allow additional treatment of 48 patients with vWD who require the pharmacotherapy with clotting factor VIII + von Willebrand factor MPs during a year.

Table 3. The results of cost analysis for the treatment of patient weighing 70 kg

Cost structure	Current treatment regimen	Simulated treatment regimen with Haemate P	Simulated treatment regimen with Wilate
The cost of the MPs	2,100,457 rub.	1,892,924 rub.	2,920,006 rub.
Dental services	40,637 rub.	38,179 rub.	58,894 rub.
Ambulance costs	3,750 rub.	2,865 rub.	2,865 rub.
Hospital treatment	21,626 rub.	21,626 rub.	21,626 rub.
Out-patient treatment	17,572 rub.	17,572 rub.	17,572 rub.
Annual medical examination	5,609 rub.	5,609 rub.	5,609 rub.
The cost of patient disability	25,368 rub.	25,368 rub.	25,368 rub.
GDP gap	131,064 rub.	131,064 rub.	131,064 rub.
Sick pays	1,800 rub.	1,800 rub.	1,800 rub.
<b>Total costs</b>	<b>2,347,883 rub.</b>	<b>2,137,007 rub.</b>	<b>3,184,804 rub.</b>

**Table 4** Distribution of patients with von Willebrand disease along the Federal Districts of the Russian Federation

Federal District	Number of patients	Number of patients requiring the treatment with von Willebrand factor MPs
Central Federal District	498	96
Southern Federal District	88	23
North-Western Federal District	2434	69
Far Eastern Federal District	7	7
Siberian Federal District	120	42
Ural Federal District	106	53
Privolzhsky Federal District	448	156
North Caucasian Federal District	45	50
<b>TOTAL</b>	<b>3746</b>	<b>496 (13%)</b>

**Conclusions**

During the pharmacoeconomic analysis of Haemate P introduction into the treatment regimens of vWD it was established that administration of Haemate P allows achieving normalization of hemostasis system parameters 30% more often and completely or partially normalize bleeding time in patients suffering from vWD in comparison with other clotting factor VIII MP containing von Willebrand factor.

Direct medical and non-medical and indirect cost analysis for the treatment of this nosology was performed at the following stages of the pharmacoeconomic analysis on the basis of the results of real clinical practice of Hematological Scientific Center of the MOH of the RF (23 patients from 5 regions of the RF) and Republican Center of Hemophilia, Saint-Petersburg (17 patients from 7 regions of the RF). It was established that the administration of Haemate P will allow cutting average cost of annual treatment course by 207,533 rub. per patient with von Willebrand disease due to a lower cost of IU of von Willebrand factor while administration of Wilate will require approximately 819,549 rub of additional costs in respect of the current treatment regimen and 1,027,082 rub in respect of Haemate P.

On the basis of the data obtained on a superior efficacy in terms of relieving of bleeding episodes of different severity with clotting factor VIII + von Willebrand factor MPs and possible average cost saving of 210,876 rub annually when switching each patient with von Willebrand disease on Haemate P, conclusion was made on its pharmacoeconomic benefit over the current treatment regimen and treatment regimen including Wilate.

The budget impact analysis performed at the next stage of the PE study (calculated for 496 patients requiring the pharmacotherapy with clotting factor VIII and Willebrand factor MPs) demonstrated that switching patients on the treatment regimen including Haemate P will allow cutting the costs of the healthcare budget by 106.4 mln rub. or by 8.91% of total costs. Saved resources of the healthcare system will allow additional treatment of 48

patients with von Willebrand disease who require the pharmacotherapy with clotting factor VIII + von Willebrand factor MPs during a year within the same budget.

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