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Clinical and Economic Aspects of the First Biosimilar Eculizumab use in Patients with Rare Diseases

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Teaser: For most orphan diseases, the lack of effective treatment remains an unsolved problem. When such drugs appear, the issue of high cost arises, which is often due to a long and complex process of their development and introduction to the pharmaceutical market.The development of biosimilar of eculizumab not only allowed for saving budget funds by cutting the cost of the medicinal product, but also for increasing the number of patients who receive essential drug therapy, and thus, for improving the quality of medical care for patients with rare diseases.

Abstract.

In March 2019, Elizaria® (JSC «GENERIUM»), the first biosimilar of eculizumab, was registered in Russia. This is the world's first experience in the release of a full-cycle biosimilar of eculizumab, including the production of a substance. Comparative non-clinical and clinical studies demonstrated the absence of toxicity, good tolerance, and comparability with the original medicinal product. Besides Russia, Elizaria® is currently registered in Belarus and Kazakhstan, and marketing activities are carried out in 14 countries. In 2019, Elizaria® already accounted for more than 75% of government purchases to provide patients with paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. The total expenses for these two rare diseases in 2020 amounted to about 8.9 billion rubles, while the introduction of a Russian biosimilar, the registered cost of which is 25% less compared to the reference medicinal product, in 2020saved about 2.6 billion rubles and helped increase the number of patients receiving the therapy.

Keywords: Eculizumab, Biosimilar, Paroxysmal Nocturnal Hemoglobinuria, Atypical hemolytic uremic syndrome, Public health, Costs

Despite the fact that rare diseases are not widespread, they have a huge impact both on the health care system and on the lifestyle of patients and their families [1]. For most orphan diseases, the lack of effective treatment remains an unsolved problem. When such medicinal products appear, the issue of high cost arises, which is often due to a long and complex process of their development and introduction to the market.

Currently, the preferential drug provision for patients with rare diseases in the Russian Federation is regulated by two programs: the first program is funded from the federal budget (Program "14 High-Cost Nosologies (HCN)" since January 2020, previously the program "7 High-Cost Nosologies" [2]), while the second program is funded from the budgets of the constituent entities of the Russian Federation ("List of life-threatening and chronic progressive

rare (orphan) diseases leading to a reduction in the life expectancy of citizens or their disability" (3).

The analysis of medicinal products for the pathogenetic treatment of rare diseases included in restrictive lists based on the State Registry of Medicines showed that as of 2018, 62 international nonproprietary names (INN) were registered in the Russian Federation, among which 90% of medicinal products are reference medicinal products and only 34% are interchangeable (4).

One example of pathogenetic therapy for rare diseases is a medicinal product that allowed for progress in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). Eculizumab is a humanized monoclonal antibody to the human complement component C5, which thanks to its high affinity inhibits the activation of the terminal complement complex. As a result, the cleavage of the C5 component into C5a and C5b and the formation of the terminal complement complex C5b-9 are completely blocked. Thereby, eculizumab restores the regulation of complement activity in the blood and prevents intravascular hemolysis in PNH patients; it also prevents the excessive activity of the terminal complex in patients with aHUS, where the cause of the disease is genetically determined dysregulation of the complement system (5).

The medicinal product by Alexion Pharma GmbH was approved by the U.S. Food and Drug Administration (FDA) in March 2007 for the treatment of PNH; in September 2011, another disease was added to the list of indications – aHUS, then the medicinal product received the status of an orphan drug. European Medicines Agency (EMA) also approved Eculizumab for the treatment of PNH in June 2007 and of aHUS – in November 2011. A little later, the Ministry of Health of Canada issued its approval: in 2009 for the treatment of PNH and in 2013 for the treatment of aHUS.

In the Russian Federation, the reference medicinal product Soliris® (INN: Eculizumab) was registered in 2011. According to the Order of the Government of the Russian Federation No. 2782r of December 30, 2014, eculizumab was included in the list of vital and essential medicinal products for medical use in 2015 [6]. In 2018, the medicinal product received the status of an orphan drug in the Russian Federation. The same year the "7 High-Cost Nosologies" program was expanded to include 12 rare diseases (7), and specifically aHUS, thus the provision of Eculizumab to patients with aHUS is now financed from the federal budget.

Eculizumab was the first medicinal product approved for each of its indications based on small-scale trials (8–10), and in 2010 it became the most expensive medicinal product in the world (11): the mean cost of an annual course was about US$ 409,500 in the United States, £ 340,200 in Great Britain, and about US$ 500,000 in Canada, and it reached 45 million rubles in the Russian Federation.

Until 2017, Alexion Pharma GmbH had exclusive rights to eculizumab, after the expiration of the patent law, one of the options for increasing the availability of drug therapy became possible due to the emergence of a biosimilar, which is a biological drug similar in quality, efficacy, and safety parameters to a reference biological drug, having the same dosage form and an identical route of administration (12).

In Russia the biotechnology companyIBC Generium LLC began the development of a biosimilar of eculizumab as part of the state program "Development of the Pharmaceutical and Medical Industry" for 2013–2020 to increase the production and provision of vital and essential domestic medicinal products (13). Comparative non-clinical studies demonstrated the absence of toxicity, good tolerance, and comparability with the original medicinal product (14,15).

In March 2019, the biosimilar ofeculizumab, medicinal product Elizaria® was registered by JSC «GENERIUM». This is the world's first experience in the release of a full-cycle biosimilar of eculizumab, including the production of a substance. The registered maximum selling price of Elizaria® was 248,258.84 rubles (excluding VAT) (US$ 3,456), which is 25% lower than that of the reference medicinal product. As part of the program of preferential drug provision to patients with rare diseases, thisprovided a greater number of patients in need of this type of treatment. Already in 2019, the share of the domestic medicinal product accounted for 54.4% of expenses within the INN eculizumab, which secured the 3rd place in the ranking of 10 INNs with the maximum increase in the share of domestic medicinal products (after INN teriflunomide and imiglucerase) (16). In the summer of 2020, after a domestic biosimilar entered the pharmaceutical market, the Swiss company Alexion Pharma GmbH decided to leave the Russian pharmaceutical market and cancel the state registration of the medicinal product.

Currently, besides the Russian Federation, Elizaria® is also registered in Belarus and Kazakhstan; the average cost of 1 package of the medicinal product in these countries is about 280 thousand rubles (~US$ 3,900). Marketing activities are underway in another 14 countries.

Epidemiology

PNH is a rare acquired disease characterized by intravascular hemolysis and hemoglobinuria (17–19). According to the Rare Disease Patient Registry, the prevalence of PNH in Russia is about 0.26 cases per 100,000 population or 380 people (the proportion of adults is 96.9%) as of January 1, 2018 (20). Among all persons with life-threatening and chronic progressive rare (orphan) diseases leading to a reduction in the life expectancy of citizens or their disability in the regional segments of the Registry, the proportion of patients with PNH is 2.2% (20). PNH is caused by a somatic mutation of the PIG-A gene; therefore, this disease is currently not curable. However, the appearance on the pharmaceutical market of Eculizumab for pathogenetic therapy made it possible to achieve significant progress in the treatment of patients with these diseases (17–19).

aHUS is an extremely rare disease of a progressive character, which is based on the uncontrolled activation of an alternative complement pathway leading to generalized microvascular thrombus formation (21). According to the Rare Disease Patient Registry, the prevalence of aHUS in Russia is about 0.28 cases per 100,000 population or 407 people (67% of pediatric patients) as of January 1, 2018 (20). Among all persons with life-threatening and chronic progressive rare (orphan) diseases leading to a reduction in the life expectancy of citizens or their disability, the proportion of patients with PNH is 2.4% in the regional segments of the Registry (20).

In 60–70% of cases, aHUS is associated with mutations in genes encoding proteins with regulation functions (factors H, I, membrane factor protein, thrombomodulin [CFH, CFI, MCP, THBD]) and activation (factors B, C3 [CFB, C3]) of an alternative complement pathway or the production of anti-CFH antibodies (AT) (22). The main target organ in this disease is the kidneys; however, in some cases, generalization of thrombotic microangiopathy (TMA), leading to the development of multiple organ failure, is possible (23–25). Until recently, transfusion of freshly frozen plasma was considered as first-line therapy for aHUS (26,27). At the end of the 20th century, significant progress was made in understanding the pathophysiology of aHUS and its treatment with pathogenetic therapy. With the introduction of Eculizumab into therapeutic practice in 2011, a new era began in the treatment of patients with aHUS (28).

Clinical efficacy and safety

A number of clinical studies have shown that the use of the reference medicinal product eculizumab in patients with PNH leads to a significant decrease in the incidence of clinical manifestations of the disease and an increase in the life quality and life span of patients (29–32).

In the open-label, prospective, non-comparative phase Ib study (ECU-PNH-Ib) (33), the safety, pharmacokinetics and pharmacodynamics of Elizaria® were assessed in previously untreated PNH patients. On the basis of 7 study sites, 11 patients were included in the full analyses set (FAS) population (8 women and 3 men), aged 26 to 75 years (mean age 40.6±15.3 years) with body mass index 17.6 to 28.0 kg/m^2. All patients were Caucasian. Ten patients (91%) completed the study without statistically significant protocol deviations and were included in the PP population (per protocol). Patients who completed the study according to the protocol, for further treatment with eculizumab, were transferred to an extended phase III study (ECU-PNH-III-X) of the safety and immunogenicity of long-term therapy with Elizaria® in PNH patients who previously participated in clinical studies of this medicinal product (extension study), approved by the Ministry of Health of the Russian Federation on May 3, 2018 (Permission No. 205) (34).

The results obtained during this clinical study (33) allowed for establishing the characteristic pharmacokinetic profile of Elizaria® during the induction of PNH therapy: the concentration of the medicinal product increases significantly by the end of the infusion (255.05 ± 46.77 µg/mL) and then gradually decreases to a minimum at the end of the dosing interval (47.09 ± 33.75 µg/mL). The mean values of the concentration of eculizumab 5 minutes before the administration of the investigational medicinal product at all visits exceeded 35 µg/mL, which is the minimum concentration sufficient for complete inhibition of intravascular hemolysis in PNH patients. Elizaria® also demonstrated its pharmacodynamic efficacy, which is manifested by a decrease in the concentration of the membrane attack complex (MAC) at the end of the first infusion of the drug, maintaining it at stable levels until visit 5. A persistent decrease in MAC concentration and a four-fold decrease in mean values of lactate dehydrogenase (LDH) by visit 5 from 1,286.4 to 280.9 U/L demonstrated a pronounced decrease in activity and stabilization of the hemolytic process as a result of induction therapy with Elizaria® at a dose of 600 mg once a week and confirmed the efficacy of the investigational medicinal product.

All 11 patients were included in the safety analysis; during the study, 9 adverse events (AEs) were reported, of which 5 episodes in 3 patients had at least a possible relationship with the investigational medicinal product. Thus, the proportion of patients with AEs associated with Elizaria® was 27.3%. In most patients, the level of seriousness of reported AEs did not exceed level 2. All AEs associated with the investigational medicinal product were classified as expected and are listed in the instructions for use of the reference medicinal product [35]. During treatment with Elizaria®, low titer binding anti-drug antibodies (ADA) were detected in two PNH patients. In both cases, there was no neutralizing activity of ADA revealed, which suggests low immunogenicity of the investigational medicinal product.

Thus, the efficacy data obtained in the study supplement the data of non-clinical studies of Elizaria® [15] and are comparable with published literature data on the reference medicinal product Soliris® (Alexion Pharma GmbH, Switzerland) in patients with PNH (29–32,35).

The efficacy and safety of Elizaria® (biosimilar) were further studied in comparison with a reference medicinal product Soliris® (originator) in a multicenter, open-label, randomized phase III study (ECU-PNH-III, NCT04463056) [36] in parallel groups in

PNH patients. The study included 32 patients who were randomized into 2 groups: group 1 received a biosimilar (n = 16), group 2 received an originator (n = 16). The dosage regimen was established taking into account the status of patients' therapy: previously untreated patients received an initial dose of 600 mg for 4 weeks, followed by maintenance therapy at a dose of 900 mg every 2 weeks; previously treated patients received a biosimilar or originator at the same dose as before the beginning of the study. The total duration of therapy was 26 weeks.

When assessing the area under the LDH concentration-time curve (LDH AUC), the mean value of LDH AUC between the groups of patients who received the biosimilar and the originator showed no statistically significant difference. Regarding the indicators of the pharmacokinetic profile (elimination half-life T½, the minimum concentration of the substance) and the pharmacodynamic parameter (MAC), there were also no statistically significant differences between the biosimilar and originator groups.

Both groups showed similar safety profiles, with a total of 13 AEs recorded in 5 patients (9 AEs in 3 patients in the biosimilar group and 4 AEs in 2 patients in the originator group). During the study, no new cases of binding ADA formation were recorded in either group.

The study results demonstrated that a biosimilar of eculizumab is comparable in terms of efficacy, safety, immunogenicity, pharmacokinetic and pharmacodynamic profile with the originator in the treatment of patients with PNH.

In foreign and domestic literature, there are also studies describing the use of the domestic biosimilar of eculizumab, medicinal product Elizaria®, in patients with aHUS of various ages (21,37,38). The published data illustrate the high efficacy of Elizaria® in the treatment of complement-mediated TMA. The patients showed stabilization of their condition over time with complete relief of clinical and laboratory signs of TMA. In clinical cases of patients with a verified diagnosis of aHUS, therapy with the Russian biosimilar medicinal product eculizumab showed its high efficacy, manifested as normalization of complete blood count indicators (platelet concentration, hemoglobin), LDH levels, as well as in a significant improvement in renal function (restoration of the urine output rate, reduction in azotemia and proteinuria). It should be noted that over the entire period of treatment, there were no cases of AEs that could be related to eculizumab therapy reported in any patient.

Post-marketing studies

Currently, 2 post-marketing prospective studies of the use of Elizaria® in PNH patients are being conducted in Russia: a prospective observational study of long-term pathogenetic therapy with Elizaria® (ECU-PNH-N01) and an open-label non-comparative post-marketing clinical study of the efficacy and safety of Elizaria® (ECU-PNH-IV) (34).

The prospective observational study ECU-PNH-N01 included 45 patients of both genders with an established PNH diagnosis in the period 2019–2021. Currently, 36 patients have completed the study. The change in LDH and hemoglobin levels over time, the incidence of thrombotic complications, the need for transfusion of erythrocyte component of donor blood, the incidence of breakthrough hemolysis in patients, changes in the PNH clone of granulocytes and erythrocytes, as well as the presence of ADAs, their titer and neutralizing activity were selected as endpoints.

In an open-label, non-comparative, post-marketing, clinical study of Elizariaefficacy and safety (ECU-PNH-IV) (34), it is planned to estimate the area under the LDH concentration-time curve (LDH AUC) during the maintenance therapy period and during 55 weeks of treatment, as well as to assess the change in hemoglobin level alterations over time, the number of

patients with a stable hemoglobin level during the period of maintenance therapy, the incidence of various thrombotic complications, the need for transfusion of erythrocyte component, the incidence of breakthrough hemolysis in patients, and changes in the PNH clone of granulocytes and erythrocytes. Over the period 2019–2021, 28 patients were enrolled in the study.

There is also one prospective observational study (ECU-aHUS-N01) of long-term therapy in patients with aHUS, which began in 2019 and is scheduled for completion in 2022, involving 8 clinical centers. The study enrolled 50 patients of both genders, pediatric and adults, with a confirmed diagnosis of aHUS. Currently, 10 patients have completed the study. During the therapy, several indicators will be assessed: the change in platelet and LDH levels over time, kidney function indicators, the incidence of TMA development, MAC level, and the presence of ADAs.

Economic aspects

The high cost of the medicinal product causes certain difficulties in its use, since, at the present stage, decision-making in the health care sector is based not only on efficacy and safety indicators but also on economic aspects.

In a number of foreign studies, an assessment of the economic feasibility of using eculizumab was carried out. Thus, in the study of Coyle D. et al., 2014 (39), the economic feasibility of using eculizumab in patients with PNH was assessed in comparison with standard medical care using the cost-effectiveness analysis. The results of this work demonstrated that the use of eculizumab is associated with higher efficacy rates (1.13 years of life and 2.45 years of quality-adjusted life-year (QALY) at a cost of CAN$ 5.24 million. The incremental cost per life year was CAN$ 4.62 million and CAN$ 2.13 million per year of quality-adjusted life. Based on the economic feasibility thresholds established in Canada, taking into account the high cost of the medicinal product, its effectiveness indicators should reach 102.3 years of quality life per 1 state-funded patient. Thus, a decrease in the cost of the medicinal product by 98.5% will lead to its economic feasibility.

This kind of studies clearly demonstrates the restrictions of classical methods of pharmacoeconomic analysis for rare diseases. On the one hand, there are data on the clinical efficacy and safety of such medicinal products, calculated in years of quality life of patients, and on the other hand, there is a long and complex process of the development and introduction of orphan drugs to the pharmaceutical market, which contributes toa rise in their price. Medicinal products for the treatment of rare diseases are a rather narrow segment of the pharmaceutical market, which leads to a situation where the reference medicinal product is often the only approach to the treatment of a particular rare disease. This leads to the fact that, given a limited budget, not all patients are able to get the treatment that they need due to its high cost.

In another foreign study by van den Brand J.A. et al., 2017 (40), a clinical and economic analysis of the use of eculizumab in patients with aHUS after kidney transplantation was carried out using classical pharmacoeconomic modeling methods (decision tree and Markov model). The results of the study have shown that the use of eculizumab after a disease recurrence is associated with a fairly high rate of effectiveness: 9.55 QALYs at a cost equal to € 425,097. At the same time, the incremental cost indicator for 1 QALY was € 18,748. Other analyzed eculizumab regimens demonstrated higher expenses with lower efficacy (Table 1). The study concluded that the use of eculizumab after a disease recurrence in patients who underwent kidney transplantation for end-stage renal failure developed as a result ofaHUS is an acceptable medical technology.

Ryan M. et al., 2020 (41) evaluated the economic impact of early prescription (in the first 7 days) of eculizumab during hospitalization of

patients with aHUS. The retrospective analysis included 222 patients with aHUS hospitalized for this disease in the period October 2011–March 2016. The early-onset therapy group included 72 patients (32.4%), the late-onset group: 150 patients (67.6%). The results of the study showed that the duration of stay in the hospital and in the intensive care unit (ICU) was significantly longer in the group of late therapy (average duration was 29.0 days compared to 16.4 days ($p < 0.001$) and 12.4 days versus 8.9 days ($p = 0.047$), respectively), and need for patients re-hospitalization within 90 days in this group was also significantly higher (36.7% ($n = 55/150$) versus 22.2% ($n = 16/72$); $p = 0.031$). Patients in the late therapy group were 3.2 times more likely to require dialysis (95% CI: 1.4–7.3). Multivariate regression analysis showed that total direct costs were US$ 103,557 in the late therapy group and US$ 85,776 in the early therapy group ($p = 0.0024$). Thus, the results of the study showed that the early prescription (in the first 7 days) of the medicinal product eculizumab during hospitalization of patients with aHUS reduces the incidence of dialysis and plasmapheresis, as well as the length of stay in the ICU and, accordingly, leads to a decrease in direct medical expenses compared with later initiation of therapy with eculizumab.

Several studies comparing the use of eculizumab and ravulizumab have been published recently (42–44). In a study by Wang Y. et al., 2020 (42), during the cost minimization analysis, it was shown that in patients with aHUS, the use of ravulizumab leads to a decrease in expenses per patient during life by 32.4% and 35.5% compared with eculizumab in adults and children, respectively. In the study by O'Connell T. et al., 2020 (43) using the Markov model, the cost-benefit analysis demonstrated that the use of the medicinal product ravulizumab in patients with PNH is associated with a higher efficacy rate (years of quality-adjusted life) and lower total expenses: the difference in efficacy was 1.67 QALY and US$ 1,673,465 in terms of expenses. Tomazos I. et al., 2020 (43) estimated the expenses of developing one of the complications of the clinical course of PNH: breakthrough hemolysis, which can occur despite the ongoing therapy. A literature review has shown that breakthrough hemolysis is often associated with an increase in LDH, aspartate aminotransferase, hemoglobinuria, the need for blood transfusions, and/or recurrence of PNH symptoms. The largest share in the costs of breakthrough hemolysis therapy in the eculizumab group is associated with a change in the medicinal product dosage regimen. The total expenses associated with the development of breakthrough hemolysis over 1 year were US$ 407 in the ravulizumab group and US$ 9,379 in the eculizumab group.

In the course of these studies, ravulizumab demonstrated its economic advantage; however, the comparison was made regarding the original medicinal product Soliris®. Wider access to the pharmaceutical market for the domestic biosimilar of eculizumab Elizaria® could influence the results of a number of pharmacoeconomic studies due to its lower cost.

In the Russian Federation, the cost of treatment of these two rare diseases (PNH and aHUS) using eculizumab was 6.1 billion rubles (US$ 84.9 million) in 2017, and 8.3 billion rubles (US$ 115.5 million) in 2018, which was about 35% of the total cost of rare diseases in the constituent entities of the country (20), by 2019 the expenses for eculizumab increased to 9.3 billion rubles (US$ 129.5 million) (45).

The arithmetic mean expenses per patient under the Rare Life-Threatening Diseases program in 2018 for the regional budget amounted to 1,067,753 rubles (US$ 14,864), and in 2020, and the expenses per patient included in theprogram registry were807,600 rubles (US$ 11,243) approximately. For the High-Cost Nosologies program, in 2018, the arithmetic mean expenses from the federal budget per patient amounted to 1,052,539 rubles (US$ 14,653), and in 2020, theexpenses

per patient were1,813,274 rubles approximately (US$ 25,243) (45). These indicators are significantly lower than the mean cost per adult patient treated with eculizumab for 1 year, using Elizaria® it amounts to 21.8 million rubles (US$ 294,992) for PHN patients and up to 29.5 million rubles (US$ 398,239) for patients with aHUS (Table 2). However, it should be noted that according to the data of the Rare Disease Patient Registry among all patients, the proportion of children with aHUS is 67% (20); in this group the dosage regimen is determined depending on the weight, thus, leading to the use of the medicinal product in lower doses.

According to the data of the unified procurement information system, 31,308 packages of eculizumab were purchased in 2019, of which Soliris® accounted for 24.6%, and Elizaria® accounted for the rest. The total expenses for two rare diseases amounted to 9.3 billion rubles (US$ 129.5 million) (20), while in 2019 alone the introduction of a domestic biosimilar saved about 1.9 billion rubles (US$ 26.5 million), of which aHUS accounted for 655 million rubles (US$ 9.1 million).

With regard to the PNH indication, the drug supply of which remained within the regional budget, there is a significant cut of costs in the budgets of constituent entities of the Russian Federation. In 2019, 19,013 packages of eculizumab were sold for this indication, of which Soliris® accounted for 4,771 packages, and Elizaria® accounted for the rest. The presence of an alternative, represented by domestic biosimilar, on the pharmaceutical market saved more than 1.2 billion rubles (US$ 16.7 million), which led to an increase in the number of patients with PNH receiving drug therapy by 10% (currently the number of patients receiving Elizaria® amounts to about 233 people, it should be noted that in 2017 only 176 patients received therapy with eculizumab [20]). At the same time, about 750 million rubles (US$ 10.4 million) from the funds saved in the regional budgets were redistributed to provide patients with other life-threatening and chronic progressive rare (orphan) diseases, which lead to a reduction in the life expectancy of citizens or their disability.

Further use of the domestic biosimilarfacilitated cost-cutting with a simultaneous increase in the proportion of patients provided with medicinal product. In2020, 32,149packages of eculizumab were purchased, and the total cost amounted to 8.9 billion rubles. If only the original medicinal product Soliris®hadbeen purchased, the expenses of federal and regional budgets wouldhave been amounted to more than 11.5 billion rubles (US$ 160.1 million), while the cost saving wasmore than 2.6 billion rubles (US$ 36.2 million) (Figure 1) (45).Thanks to the launch of Elizaria® to the pharmaceutical market,in 2020, JSC «GENERIUM»was ranked the second among20 major manufacturers of medicinal products in the segment of preferential provision of medicines (a company's share was 3.1%), while, the medicinal product itself was ranked the second among 20 drugs in terms of a share of costs for preferential provision of medicines (3.1% share) (46).

Currently, the pricing policy implemented in the Russian Federation is aimed at improvement of the accessibility of highly effective drug therapies to the population and reducing the burden on both the federal budget and the regional budget of the health care system. Based on the assessment of the Russian pharmaceutical market in 2020, about 3,343million rubles (US$ 45.1 million) were spent onpurchase of Elizaria® under the High-Cost Nosologies program, and 3,814 million rubles (US$ 51.5 million) as part of the regional program (46). Therefore, the cost reduction for INN eculizumab became one of the main opportunities for costcutting for the budget of the High-Cost Nosologies program (besides tacrolimus and lenalidomide) (47). Currently, one of the most urgent problems in the field of drug supply throughout the world and in the Russian Federation, in particular, is the policy of drug provision for patients with rare diseases. An insufficient number of clinical

and pharmacoeconomic studies of adequate quality hinder the decision-making on the financing of these diseases. And so far, a single instrument for a comprehensive assessment of the consequences of the use of medicinal products for the treatment of patients with rare diseases, taking into account clinical and economic indicators, has not been developed for general practice. Currently, in many countries, alternative ways of increasing the availability of drug therapy for rare diseases are actively used: the introduction of interchangeable medicinal products, biosimilars, or cheaper reference medicinal products.

Conclusions

The project for the development of domestic biosimilar of eculizumab Elizaria® implemented as part of the state program "Development of the Pharmaceutical and Medical Industry" not only allowed for saving budget funds by cutting the cost of the medicinal product, but also for increasing the number of patients who receive essential drug therapy, and thus, for improving the quality of medical care for patients with rare diseases.

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