SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Elizaria 300 mg, concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Eculizumab (rEclz), a humanized antibody produced in CHO F5A7 cell line using recombinant DNA technology.
Each vial of 30 mL contains 300 mg of Eculizumab (10.0 mg/mL).
Excipients to be considered in the medicinal product composition: sodium — 5 mmol (115 mg) (see section 4.4).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colorless liquid.

4. CLINICAL DATA

4.1. Therapeutic indications

Elizaria is indicated for treatment of adult and pediatric patients with:

- paroxysmal nocturnal hemoglobinuria (PNH). The efficacy of eculizumab has been confirmed in patients with hemolysis and concomitant clinical symptoms evidencing a highly active disease, regardless of the need for blood transfusions in history;
- atypical hemolytic uremic syndrome (aHUS).

Elizaria is indicated for the treatment of adult patients with:

- refractory generalized myasthenia gravis (GMG) with anti-acetylcholine receptor (AChR) antibodies;
- recurrent neuromyelitis optica spectrum disorders (NMOSD) with anti-aquaporin-4 antibodies (AQP4).

4.2. Posology and method of administration

Posology

Elizaria should be administered by qualified healthcare professionals under the supervision of physicians experienced in the management of patients with hematological, renal, neuromuscular, or neuroinflammatory diseases.

Adult patients

Paroxysmal nocturnal hemoglobinuria (PNH)

The posology for adult patients (≥18 years of age) includes a 4-week initial cycle followed by the phase of maintenance therapy.

Initial cycle: 600 mg of Elizaria by intravenous drip infusion for 25–45 minutes (35 ± 10 minutes) once a week for the first 4 weeks.

Maintenance therapy phase: 900 mg of Elizaria by intravenous drip infusion for 25–45 minutes (35 ± 10 minutes) at Week 5, followed by 900 mg of Elizaria by intravenous drip infusion for 25–45 minutes (35 ± 10 minutes) every 14 days ± 2 days.

Atypical hemolytic uremic syndrome (aHUS), refractory generalized myasthenia gravis (GMG), and neuromyelitis optica spectrum disorders (NMOSD)

The posology for adult patients (≥18 years) includes a 4-week initial cycle followed by the phase of maintenance therapy.

Initial cycle: 900 mg of Elizaria by intravenous drip infusion for 25–45 minutes (35 ± 10 minutes) once a week for the first 4 weeks.

Maintenance therapy phase: 1,200 mg of Elizaria by intravenous drip infusion for 25–45 minutes (35 ± 10 minutes) at Week 5, followed by 1,200 mg of Elizaria every 14 days ± 2 days.

Pediatric patients

Treatment of pediatric patients with PNH or aHUS weighing ≥40 kg is carried out in accordance with the posology recommendations for Elizaria for adult patients with relevant diseases.

In pediatric patients with PNH or aHUS weighing below 40 kg, the dose of Elizaria is determined depending on the child's weight:

Patient's weight	**Initial cycle**	**Maintenance therapy phase**
30 to <40 kg	600 mg once a week × 2	900 mg at Week 3; followed by 900 mg every 2 weeks
20 to <30 kg	600 mg once a week × 2	600 mg at Week 3; followed by 600 mg every 2 weeks
10 to <20 kg	600 mg once a week × 1	300 mg at Week 2; followed by 300 mg every 2 weeks
5 to <10 kg	300 mg once a week × 1	300 mg at Week 2; followed by 300 mg every 3 weeks

No studies of administration of eculizumab in patients with PNH with body weight below 40 kg have been conducted. Eculizumab dose selection for these patients is based on the eculizumab posology for patients with aHUS and weighing below 40 kg.

No clinical studies of eculizumab in pediatric patients with refractory GMG and NMOSD have been conducted.

Additional administration of the medicinal product

For adult patients with aHUS, refractory GMG, NMOSD, and pediatric patients with aHUS, an additional dose of Elizaria is required in case of plasmapheresis, plasma exchange transfusion or fresh frozen plasma infusion:

Procedure type	**Most recent Elizaria dose**	**Additional Elizaria dose after each procedure**	**Timing of additional Elizaria dose**
Plasmapheresis or plasma exchange transfusion	300 mg	300 mg per each plasmapheresis or plasma exchange transfusion	Within 60 minutes after each plasmapheresis or plasma exchange transfusion
	≥600 mg	600 mg per each plasmapheresis or plasma exchange transfusion	
Fresh frozen plasma transfusion	≥300 mg	300 mg per unit of fresh frozen plasma	60 minutes before transfusion of each unit of fresh frozen plasma

Treatment monitoring

Patients with aHUS should be monitored for symptoms of thrombotic microangiopathy (TMA) (see section 4.4). Life-long treatment with Elizaria is recommended, unless there are medical indications for treatment discontinuation (see section 4.4).

According to the available data, during the treatment of refractory GMG, a clinical response is usually achieved by Week 12 of treatment with eculizumab. Discontinuation of therapy should be considered if there is no evidence of therapeutic effect in patients at Week 12.

Special populations

Elderly patients

Elizaria may be prescribed to patients over 65 years of age.

Special dosing regimens and special precautions are not required, although clinical experience with treatment in this age group is limited.

Patients with renal impairment

No adjustment of Elizaria dose is required in this group of patients.

Patients with hepatic impairment

No special studies of Elizaria efficacy and safety in patients with hepatic impairment have been conducted.

Method of administration

Bolus administration of the medicinal product is strictly prohibited. Elizaria can only be administered via an intravenous infusion, in accordance with the description below.

See instructions for preparation of the medicinal product infusion solution in section 6.6.

The prepared solution of Elizaria should be administered by intravenous infusion for 25–45 min (35 ± 10 minutes) in adult patients and for 1 to 4 hours in pediatric patients under 18 years.

For intravenous administration of the prepared Elizaria solution, it is necessary to use special infusion systems with controlled delivery. During administration there is no need to protect the prepared solution of the medicinal product from light.

The solution for infusion should be used immediately after preparation. Unused solution should be disposed of.

After the end of the medicinal product administration, patient monitoring should continue for 1 hour. If adverse events develop during the medicinal product administration, the infusion rate can be reduced down to a complete stop of the injection at the discretion of the physician. When reducing the rate of Elizaria injection, the total infusion time should not exceed 2 hours for adult patients and 4 hours for pediatric patients under 18 years of age.

4.3. Contraindications

- Hypersensitivity to eculizumab or any excipient listed in section 6.1.
- Absence of vaccination against Neisseria meningitidis (in the absence of the relevant prophylactic antibiotic therapy within 2 weeks after vaccination).
- Active Neisseria meningitidis infection.

4.4. Special warnings and precautions for use

With caution

Taking into account the mechanism of action of Elizaria, it should be prescribed with caution to patients with:

- active systemic infections;
- hepatic impairment (due to the absence of clinical experience).

Eculizumab therapy does not affect the aplastic component of anemia in patients with PNH.

Meningococcal infection

The mechanism of action of Elizaria suggests an increased risk of developing of meningococcal infection (Neisseria meningitidis) on the background of its use. Any serotypes including atypical ones, e.g., X, can be considered as pathogenic serotypes. In order to decrease the potential of infection, all patients should be immunized with meningococcal vaccine within 2 weeks prior to initiation of therapy with Elizaria. Patients who started treatment with Elizaria earlier than 2 weeks after vaccination against meningococcal infection should receive appropriate preventive antibacterial treatment during 2 weeks after vaccination. All patients should also be revaccinated according to the standards existing in the Russian Federation. Vaccines against meningococcal serotypes A, C, Y, W135, and B (if available) are recommended. In some cases, vaccination does not provide sufficient protective action.

The official guidelines should be strictly followed when selecting an antibiotic for the treatment of meningitis.

It is necessary to instruct patients that in case of body temperature elevation, development of headache with fever and/or stiff neck or light sensitivity, they should immediately seek medical attention because these signs can be suggestive of meningococcal infection.

Other systemic infections

The mechanism of action of Elizaria also suggests the possibility of latent infection activation, although the data of clinical studies did not reveal any differences in the frequency, severity or localization of infections in patients who received eculizumab and placebo. Nevertheless,

patients should be warned about the possibility of activation of the infection during treatment with Elizaria and its possible symptoms.

Infusion reactions

Intravenous administration of Elizaria, as well as administration of other protein products, may be accompanied by hypersensitivity reactions including anaphylaxis. Despite the lack of clinical data on the development of such reactions during treatment with eculizumab, administration of the medicinal product should be discontinued in case of a severe infusion reaction, and symptomatic therapy should be prescribed.

Immunogenicity

Low anti-drug antibody (ADA) titer was determined in patients who received treatment both with eculizumab (3.4 %) and placebo (4.8 %). Anti-eculizumab antibodies were detected in 3 % of patients with aHUS who received eculizumab.

Neutralizing anti-eculizumab antibodies were detected in 1 of 100 (1 %) patients with aHUS. In patients with refractory GMG, no anti-eculizumab antibodies were detected in clinical studies after 26 weeks of active treatment. In a placebo-controlled study in patients with NMOSD, a low titer of non-persistent anti-eculizumab antibodies without neutralizing activity was determined in 2/96 (2 %) patients treated with eculizumab. No correlation was found between ADA titer and clinical efficacy of the medicinal product or its side effects.

Immunization

Vaccination can additionally activate complement, resulting in increased manifestations of the underlying disease in patients with complement-mediated diseases, including PNH, aHUS, refractory GMG and NMOSD, such as hemolysis (in patients with PNH), TMA (in patients with aHUS), a relapse of refractory GMG, or a relapse of NMOSD symptoms. Therefore, after the recommended vaccination, patients should be closely monitored for symptoms of the disease.

Before initiation of therapy with Elizaria, all patients with PNH, aHUS, refractory GMG, and NMOSD are recommended to receive complete vaccination in accordance with the national schedule for preventive vaccinations. In addition, all patients must receive meningococcal vaccine at least 2 weeks before the start of treatment with Elizaria. Vaccines against serotypes A, C, Y, W135 and B (if available) are recommended for prevention of meningococcal infection.

Patients under 18 years should also be vaccinated against Haemophilus influenzae and pneumococcus in strict compliance with the national immunization schedule.

Anticoagulation therapy

Recommendations for anticoagulation therapy should not be changed due to prescription of Elizaria.

Treatment with immunosuppressants and anticholinesterase agents

The patients with refractory GMG in clinical studies of eculizumab continued treatment with immunosuppressants and anticholinesterase agents. In an open-label extension study, the daily

dose of at least one immunosuppressant was reduced in 47% of patients due to the relief of MG symptoms on treatment with eculizumab. When reducing the dose or discontinuing the use of immunosuppressants and anticholinesterase agents, patients should be closely monitored for signs of disease exacerbation.

The patients with NMOSD who participated in the clinical study continued treatment with concomitant immunosuppressants while on treatment with eculizumab. The cases of immunosuppressive therapy discontinuation were not analyzed in the study. If the immunosuppressant is discontinued or its dose is reduced, the patients should be closely monitored for signs or symptoms of a potential relapse of NMOSD.

Laboratory monitoring of patients with PNH

To monitor the severity of intravascular hemolysis in patients with PNH during treatment with Elizaria it is necessary to determine the activity of lactate dehydrogenase (LDH) in blood serum. In cases where dose adjustment is necessary during the period of maintenance therapy, frequency of the medicinal product administration defined by the range of 14 ± 2 days can be increased up to once every 12 days.

Laboratory monitoring of patients with aHUS

TMA should be monitored in patients with aHUS during treatment with Elizaria using regular monitoring of platelet count and activity of lactate dehydrogenase and creatinine in blood serum. In cases where dose adjustment is necessary during the period of maintenance therapy, frequency of the medicinal product administration defined by the range of 14 ± 2 days can be increased up to once every 12 days.

Treatment discontinuation in patients with PNH

In case of discontinuation of therapy with Elizaria, patients should be monitored to provide control of intravascular hemolysis intensity. Signs of severe hemolysis are: serum LDH activity higher than that before initiation of therapy with Elizaria, in combination with one of the following parameters: PNH cell population declines by more than 25 % (in absence of a dilution effect in case of blood transfusion) within 1 week or earlier; hemoglobin concentration below 50 g/L or its decrease by more than 40 g/L within 1 week or earlier; development of angina pectoris or an increase in its severity; mental disorders; increase in blood creatinine concentration by 50 % or thrombosis. The duration of follow-up in patients after discontinuation of treatment with Elizaria should be at least 8 weeks.

In case of signs of severe hemolysis after therapy discontinuation, it is recommended to prescribe blood transfusion (red blood cell mass) or to perform blood exchange transfusion if, according to flow cytometry data, PNH cell population is >50 % of the total red blood cell count, and also to prescribe anticoagulants, corticosteroids or resume therapy with Elizaria. Follow-up data of 16 patients with PNH in whom eculizumab therapy was discontinued did not reveal an increase in intensity of intravascular hemolysis.

Treatment discontinuation in patients with aHUS

After discontinuation of treatment with eculizumab, recurrence of TMA symptoms was noted in some patients with aHUS 4 to 127 weeks after discontinuation of therapy. In clinical studies

of aHUS, a total of 61 patients (21 of them — pediatric patients) stopped using eculizumab, and the average follow-up period was 24 weeks. After discontinuation of treatment, fifteen serious complications associated with relapse of TMA were reported in 12 patients. Two more cases of severe TMA manifestations occurred in 2 patients who received eculizumab at a lower dose, outside the approved dosing regimen. Serious manifestations of TMA were observed in patients regardless of identified genetic mutations, high risk of polymorphism, or autoantibodies. These patients had additional serious medical complications, including: rapid deterioration in renal function, diseases requiring hospitalization and progression of chronic kidney disease (CKD) to end-stage renal disease requiring renal replacement therapy.

Despite the resumption of treatment with eculizumab, progression of the condition to end-stage renal failure was observed in one patient. After discontinuation of treatment with eculizumab, the patients with aHUS should be closely monitored for signs and symptoms of severe thrombotic microangiopathy complications. Monitoring may be insufficient to predict or prevent severe thrombotic microangiopathy complications in patients with aHUS after discontinuation of the medicinal product.

Signs of TMA manifestations after discontinuation of eculizumab are: (1) any two or re-detectable changes in one of the following parameters: a reduction in platelet count by ≤ 25 %, compared to the baseline or the maximal platelet count during treatment with eculizumab; an increase in serum creatinine concentration by ≥ 25 %, compared to the baseline or the minimal level during eculizumab therapy; or an increase in serum LDH activity by ≥ 25 %, compared to the baseline or the minimal value during eculizumab therapy; or (2) any of the following symptoms: mental changes, convulsions, angina pectoris, shortness of breath, thrombosis.

In case of development of severe TMA complications after discontinuation of treatment with eculizumab, it is recommended to resume therapy with eculizumab, prescribe maintenance treatment using plasmapheresis or plasma exchange transfusions or appropriate specific maintenance therapy including hemodialysis, artificial respiration or anticoagulation therapy.

Discontinuation of treatment for refractory GMG

In the treatment of refractory GMG, eculizumab was used only in the setting of chronic administration. The patients who discontinued the use of eculizumab should be closely monitored for the timely detection of signs and symptoms of their condition aggravation.

Discontinuation of treatment for NMOSD

The use of eculizumab for the treatment of NMOSD was studied only in the setting of chronic administration, and the effect after treatment discontinuation has not been described yet. The patients who discontinued the use of eculizumab should be closely monitored for the timely detection of signs and symptoms of NMOSD aggravation.

Excipients

Each vial of the medicinal product contains 5 mmol (115 mg) of sodium. This should be considered in patients on a low-sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

No studies of interactions of eculizumab have been performed.

Elizaria may only be mixed with 0.9 % sodium chloride solution, 0.45 % sodium chloride solution or 5 % dextrose (glucose) solution for injection.

Long-term treatment with human immunoglobulin (IVIg) products may decrease eculizumab concentration in blood of patients due to the FcRn receptor blocking mechanism. No studies of drug interaction of eculizumab in patients receiving IVIg products have been performed.

4.6. Fertility, pregnancy and lactation

Women of childbearing age should use reliable methods of contraception during treatment with Elizaria and for 5 months after its completion.

Pregnancy

No controlled studies of the use of eculizumab during pregnancy have been performed. Limited data on the use of eculizumab during pregnancy (less than 300 pregnancy outcomes) suggest that it does not affect the frequency of risk of fetal damage and/or embryotoxicity.

It is known that human immunoglobulin G (IgG) penetrates the placental barrier; therefore, eculizumab can inhibit the complement's terminal activity in the fetal blood. Elizaria should not be used during pregnancy, except for cases when the benefit to the mother outweighs the potential risk to the fetus.

Lactation

It has not been established whether eculizumab is excreted in breast milk, but, taking into account the potential adverse effects of the medicinal product, it is recommended to discontinue breastfeeding during the treatment and for 5 months after its completion.

Fertility

No data on the effect on male or female fertility have been obtained during performed studies.

4.7. Effects on the ability to drive and use machines

Treatment with Elizaria have no effect on the ability to drive and use machines; however, given the possibility of adverse reactions during treatment with the medicinal product (e.g., headache, dizziness, weakness), caution should be exercised when driving and using machines.

4.8. Adverse reactions

Summary of adverse reactions

Data on the safety of eculizumab were obtained from 31 clinical studies in which 1,503 patients with various complement-mediated diseases, such as PNH, aHUS, refractory GMG, and NMOSD, were treated with the medicinal product. The most common adverse event associated with the eculizumab treatment was a headache (noted mainly during the initial cycle of therapy). The most severe adverse event was meningococcal sepsis.

Tabulated summary of adverse reactions

A summary of adverse reactions observed during clinical studies of eculizumab, as well as in the post-marketing period in patients with PNH or aHUS, refractory GMG, and NMOSD, classified by system organ class (MedDRA) and by frequency of occurrence according to

WHO: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) are provided below.

Organs and systems	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**
Infections and infestations		Pneumonia, infections of the upper respiratory tract, bronchitis, nasopharyngitis, urinary tract infections, oral herpes	Meningococcal infection[a], sepsis, septic shock, peritonitis, lower respiratory tract infections, bronchitis, fungal infections, viral infections, abscess[c], inflammation of the subcutaneous tissue, influenza, gastrointestinal infections, cystitis, infections, sinusitis	Aspergillosis[b], bacterial arthritis[b], gonococcal infections of the urogenital tract, infections caused by *Haemophilus influenzae*, impetigo, gingivitis
Benign, malignant and unspecified neoplasms (including cysts and polyps)				Myelodysplastic syndrome, melanoma
Blood and lymphatic system disorders		Leukopenia, anemia	Thrombocytopenia, lymphopenia	Hemolysis*, abnormal blood coagulation factor, erythrocyte agglutination, coagulopathy
Immune system disorders			Anaphylactic reactions, hypersensitivity reactions	
Endocrine disorders				Hyperthyroidism
Metabolism and nutrition disorders			Loss of appetite	
Psychiatric disorders		Insomnia	Depression, anxiety, mood swings	Abnormal dreams, sleep disorders
Nervous system disorders	Headache	Dizziness, dysgeusia	Paresthesia, tremor	Syncope

Organs and systems	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**
Eye disorders			Blurred vision	Conjunctival irritation
Ear and labyrinth disorders			Tinnitus, vestibular vertigo	
Cardiac disorders			Palpitation	
Vascular disorders		Arterial hypertension	Malignant hypertension, arterial hypotension, hot flashes, venous disorders	Hematoma
Respiratory, thoracic and mediastinal disorders		Cough, pain in the larynx and pharynx	Dyspnea, nose bleeding, itchy throat, nasal congestion, rhinorrhea	
Gastrointestinal disorders		Abdominal pain, diarrhea, nausea, vomiting	Abdominal distention, constipation, dyspepsia	Gastroesophageal reflux, gum pain
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders		Alopecia, pruritus, rash	Urticaria, erythema, petechiae, hyperhidrosis, dry skin	Dermatitis, skin depigmentation
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia	Muscle spasms, bone pain, back pain, neck pain, joint swelling, pain in the limbs	Trismus
Renal and urinary disorders			Impaired renal function, dysuria, hematuria	
Reproductive system and breast disorders			Spontaneous erection	Menstrual disorder

Organs and systems	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**
General disorders and administration site conditions		Fever, weakness, flu-like syndrome	Edema, chest discomfort, asthenia, pain in the chest, chills, pain at the administration site	Extravasation, paresthesia at the administration site, hot flashes
Investigations			Elevated aspartate aminotransferase, elevated alanine aminotransferase and gamma glutamyl transferase, decreased hemoglobin and hematocrit	Positive Coombs test[b]
Injury, poisoning and procedural complications			Non-specific administration site reactions	

[*] – detailed information is provided in the Description of Specific Adverse Reactions subsection;

[a] – meningococcal infections include the following group: meningococcal sepsis, meningococcal meningitis, Neisseria infection;

[b] – adverse reactions identified in the post-marketing period;

[c] – abscesses occurred in the following locations (the preferred term MedDRA is given): limb abscess, colon abscess, kidney abscess, subcutaneous abscess, tooth abscess, hepatosplenic abscess, perirectal abscess, rectal abscess.

The presented data were obtained during clinical studies of the reference product Soliris for the following indications: bronchial asthma, aHUS, dermatomyositis, generalized myasthenia gravis, neuromyelitis optica spectrum disorders, paroxysmal nocturnal hemoglobinuria, psoriasis, rheumatoid arthritis, interstitial membranous glomerulonephritis.

Description of specific adverse reactions

The most severe side effect reported in all clinical studies in PNH or patients with aHUS was meningococcal septicemia. Cases of infection with other Neisseria species have been reported, including sepsis with Neisseria gonorrhoeae, Neisseria sicca/subflava, Neisseria spp. unspecified.

Anti-eculizumab antibodies were detected in 2 % of patients with PNH and 3 % of patients with aHUS who received treatment with the medicinal product. Antibody formation is typical of therapy with any protein medicinal products.

Cases of hemolysis were noted if an eculizumab dose was missed or delayed in patients with PNH.

The clinical manifestations of thrombotic microangiopathy were noted if an eculizumab dose was missed or delayed in patients with aHUS.

Pediatric patients

A pooled safety analysis found no differences in the safety profiles in children aged 11 to 18 years and adult patients with PNH. In children, the headache was the most common adverse event.

According to the studies, the safety profile in children aged 2 months to 18 years was not different from that in adult patients with aHUS.

No clinical studies of eculizumab in pediatric patients with refractory GMG and NMOSD have been conducted.

Elderly patients

There were no differences in the safety profile between elderly patients (> 65 years) and younger patients with refractory GMG.

Patients with other medical conditions

Additional safety data were obtained in 12 completed clinical studies involving 934 patients who received eculizumab for the pathogenetic therapy of conditions other than PNH, aHUS, refractory GMG, or NMOSD. The profile of adverse reactions during treatment with eculizumab in patients with the diseases investigated in these studies did not differ from the indications already reported. One patient with idiopathic membranous glomerulonephritis was not vaccinated before therapy initiation and had meningococcal meningitis.

In a clinical study of the use of Elizaria in acute respiratory distress syndrome along with a new coronavirus infection COVID-19, three serious fatal adverse reactions were reported: “Respiratory failure” (1 case), “Multiple organ failure” (2 cases). Also, in this study, two serious adverse reactions “Inflammatory Reaction Syndrome” were recorded; in both cases, these reactions did not resolve, and discontinuation of the medicinal product was required.

Reporting suspected adverse reactions

It is important to report suspected adverse reactions after authorization of the medicinal product for the purpose of continuous monitoring of the risk/benefit ratio. Healthcare professionals are recommended to report any suspected adverse reactions to the medicinal product using national adverse reaction reporting systems of the Eurasian Economic Union member states.

The contact details of the authorized organizations of all the EAEU member states, where the authorization of the medicinal product is planned, are presented below:

Russian Federation
Federal Service for Surveillance in Healthcare
(Roszdravnadzor)
http://roszdravnadzor.ru

4.9. Overdose

Cases of eculizumab overdose are unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants; selective immunosuppressants.

ATC code: L04AA25

Elizaria is a biosimilar medicinal product.

Mechanism of action

Eculizumab inhibits the activity of the human terminal complement complex, binding to its C5 component with high affinity. As a result, the cleavage of C5 component into C5a and C5b and the formation of C5b-9 complement terminal complex are completely blocked. Thus, eculizumab restores the regulation of complement activity in blood, prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH), and also prevents the excessive activity of the terminal complex in patients with atypical hemolytic uremic syndrome (aHUS), refractory generalized myasthenia gravis (GMG), neuromyelitis optica spectrum disorders (NMOSD), where the disease is caused by genetically determined complement system disorder.

Pharmacodynamic effects

Treatment with Elizaria is accompanied by a rapid and stable decrease in the terminal complement complex activity. In most patients with PNH, eculizumab plasma concentration is about 35 μg/mL which is sufficient for complete inhibition of intravascular hemolysis induced by activation of the terminal complement complex. Chronic uncontrolled complement activation inducing the development of thrombotic microangiopathy (TMA) is also blocked by eculizumab in patients with aHUS. A rapid and stable decrease in the terminal complement complex activity was observed in all aHUS patients receiving eculizumab in the recommended doses, and a plasma concentration of about 50–100 μg/mL was sufficient to completely inhibit the terminal complement complex activation.

In patients with refractory GMG, uncontrolled activation of the terminal complement component causes membrane attack complex (MAC)-mediated lysis and C5a-associated inflammation at the neuromuscular junction (NMS), which leads to impaired neuromuscular transmission. Chronic use of eculizumab leads to complete and sustained suppression of the terminal complement component activity.

In patients with neuromyelitis optica spectrum disorders (NMOSD), uncontrolled terminal activation of complement induced by autoantibodies to aquaporin-4 leads to the formation of MAC and C5a-mediated inflammation, which causes necrosis of the astrocytes and increased permeability of the hematoencephalic barrier, and also, results in death of surrounding oligodendrocytes and neurons. Chronic use of eculizumab leads to immediate, complete and sustained suppression of the terminal complement component activity.

On the other hand, the deficiency of the terminal complement complex is accompanied by an increased incidence of infection caused by encapsulated microorganisms, mainly meningococcal infections. At the same time, eculizumab maintains the level of early complement activation products required for the opsonization of microorganisms and immune complex removal.

The experimental results have indicated no cross-reactivity or signs of reproductive toxicity. The genotoxicity of eculizumab, its carcinogenicity, and the effect on fertility in animals have not been studied.

Clinical efficacy and safety

Paroxysmal nocturnal hemoglobinuria

The efficacy and safety of eculizumab in patients with PNH with signs of hemolysis were assessed in a double-blind, placebo-controlled 26-week study (87 patients), 52-week open-label, non-randomized study (97 patients) as well as open-label extension study which included patients from the first two studies and 11 patients from a phase II study.

A significant stable decrease (by 86 %, $p < 0.001$) of intravascular hemolysis evaluated by lactate dehydrogenase (LDH) activity was observed in patients receiving eculizumab. As a result, the intensity of anemia decreased, which was confirmed by the stabilization of hemoglobin levels and reduction in the requirement for blood transfusion. Patients noted a reduction in fatigue and an improvement in the quality of life. A reduction in the frequency of thromboembolic complications has been observed.

In the international PNH Registry observational study, the efficacy of eculizumab therapy was evaluated in patients without a history of blood transfusions but with active hemolysis confirmed by an increase in LDH level 1.5 times higher than the upper limit of normal and the presence of associated clinical symptoms: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin < 100 g/L), severe vascular complications (including thrombosis), dysphagia or erectile dysfunction.

The study has shown that administration of eculizumab in such patients was accompanied by a significant ($p < 0.001$) decrease in hemolysis (the evaluation was carried out by LDH level decrease) and a decrease in associated clinical symptoms, including fatigue.

Atypical hemolytic uremic syndrome

The efficacy and safety of eculizumab have been studied in prospective clinical studies in the adult and pediatric populations with a total of 100 patients. Two groups of patients participated in the studies: patients with newly diagnosed aHUS and signs of TMA (thrombocytopenia

below 150,000/μL, LDH and creatinine above the upper limit of normal), as well as patients with a long-term aHUS without obvious hematological manifestations of TMA.

During treatment with Eculizumab, all patients achieved a decrease in the activity of the terminal complement complex and normalization of platelet count (according to two studies, in 82 % and 90 % of patients, respectively) which was maintained for two years (88 % and 90 %, respectively). The therapy led to the inhibition of complement-mediated TMA and the absence of TMA symptoms (in 80 % and 88 % of patients, respectively) which maintained for two years: in 88 % and 95 % of patients, respectively.

During therapy with eculizumab, a significant improvement in renal function evaluated by the estimated glomerular filtration rate (eGFR) was observed: improvement in eGFR >15 mL/min/1.73 m^2 was observed in both studies in 47 % and 53 % of patients, respectively, and was maintained for two years in 59 % and 40 % of patients, respectively. Normalization of hematological parameters was achieved in both studies in 76 % and 90 % of patients, respectively, in both studies with a positive trend over two years in 88 % and 90 % of patients, respectively.

Refractory generalized myasthenia gravis

The efficacy and safety of eculizumab in patents with refractory generalized myasthenia gravis have been proven in two prospective controlled studies involving 139 patients. In one double-blind, randomized study, 118 patients with persistent symptoms of the disease with previous therapeutic failure were treated with eculizumab or placebo for 26 weeks. All patients had antibodies to acetylcholine receptors (AChR) corresponding to MG severity classes II-IV and more than 6 points according to the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale. The criteria for refractoriness were defined as lack of treatment effect of two or more immunosuppressants for at least one year and the need for periodic plasma exchange transfusions or administration of immunoglobulins to control the disease symptoms. The proportion of patients with a clinical response at Week 26 (improvement by at least 3 points on the MG-ADL scale) without additional rescue therapy was 59.7 % for patients receiving eculizumab, compared to 39.7 % in the placebo group (p = 0.0229). The proportion of clinical responses (improvement by at least 5 points) according to the QMG quantitative scale, which takes into account the strength of individual muscle groups, without the need for additional rescue therapy, was 45.2 % in the eculizumab group versus 19 % in the placebo group (p = 0.0018). All patients who continued to treatment with eculizumab as part of the open-label study showed a positive response for all indicators: MG-ADL, QMG, MGC (Myasthenia Gravis Composite scale), MG-QoL15 (15-item Myasthenia Gravis Quality of Life Questionnaire) for another 52 weeks.

In clinical studies, treatment with eculizumab was received by 22 elderly patients (aged > 65 years) with refractory generalized myasthenia gravis. There were no significant differences in efficacy and safety associated with age.

No studies of eculizumab use in pediatric patients with refractory generalized myasthenia gravis have been conducted.

Neuromyelitis optica spectrum disorders (NMOSD)

The efficacy of eculizumab in NMOSD was confirmed in a prospective controlled clinical study involving 143 patients, 119 of whom continued treatment with eculizumab in an open-label study to assess its long-term efficacy and safety. The study involved patients with an established diagnosis of NMOSD, the presence of antibodies to aquaporin-4, with a history of at least 2 relapses in the past 12 months or 3 relapses in the past 24 months and the EDSS score ≤ 7 points. If required, the patients received therapy with immunosuppressants, other than mitoxantrone or rituximab. A pronounced effect of eculizumab with regard to the time to the first exacerbation (assessed by the Independent Committee for Exacerbation Evaluation) compared to placebo (a relative risk reduction of exacerbation was 94 %, the risk ratio was 0.058, $p < 0.0001$). Therapy with eculizumab led to an improvement in the time to exacerbation, regardless of concomitant treatment with immunosuppressants. The ratio of the average annual frequency of exacerbations during treatment with eculizumab compared to placebo was 0.045 (90 % CI, 0.013,0.0151), representing a relative risk reduction of 95.5 % ($p < 0.0001$). Compared to the placebo group, patients treated with eculizumab also showed a reduction in the average annual rate of hospitalizations (0.04 for eculizumab versus 0.31 for placebo), a reduction in the frequency of corticosteroid use to relieve exacerbations (0.07 versus 0.42), or plasma exchange transfusion therapy (0.02 versus 0.19). At the end of treatment, the group of patients receiving treatment showed an advantage compared to placebo for all secondary efficacy criteria: EDSS (Extended Disability Status Scale), mRS, HAI (Functional Activity Assessment Scale), EQ5-5D (European Quality of Life scale), VAS (Visual Analog Scale of pain).

No studies of eculizumab for the treatment of exacerbations of NMOSD have been conducted.

No studies of eculizumab in pediatric patients with NMOSD have been conducted.

Comparative efficacy and safety of Elizaria

A comparative assessment of the efficacy and safety of Elizaria and the reference product Soliris (Alexion Pharma GmbH, Switzerland) was carried out in 32 patients with paroxysmal nocturnal hemoglobinuria as part of a 26-week clinical study. The intensity of intravascular hemolysis by the value of the area under the LDH concentration-time curve (LDH AUC) was estimated during the period of maintenance therapy. The analysis showed similar LDH AUC values ($p > 0.05$) in both treatment groups. The mean LDH AUC values were 62,957.6 ± 46,066.5 U/L × days (95 % CI [38,410.4; 87,504.7]) in the Elizaria group and 47,085.9 ± 25,521.8 U/L × days (95 % CI [33,486.2; 60,685.5]) in the Soliris group. The one-sided 95 % confidence interval for the difference in LDH AUC between groups was 13,255.0 U/L × days (one-sided 95 % CI [-10,492.9; 37,002.8]) in the population of patients who completed the study without deviating from protocol procedures, which is about 12.3 % of the previously identified placebo-controlled effect of the reference product Soliris.

In the compared groups, comparable changes ($p > 0.05$) were obtained for all declared secondary efficacy endpoints. The mean change in hemoglobin level was 2.4 ± 14.3 g/L (95 % CI [-5.2; 10.1]) in the Elizaria group and 2.8 ± 13.1 g/L (95 % CI [-4.2; 9.7]) in the Soliris

group. Stabilization of hemoglobin levels during the maintenance therapy period was achieved in 6 of 16 patients (37.5 %) in the Elizaria group and in 2 of 14 patients (14.3 %) in the Soliris group ($p > 0.05$).

During the study, one thrombotic complication (thrombophlebitis) was reported in the Soliris group. There were no differences between the groups in the need for blood transfusions: 2 out 16 patients (12.5 %) in the Elizaria group and 5 out 16 (31.3 %) in the Soliris group ($p > 0.05$). During the entire study period, 4 cases of breakthrough hemolysis were reported in 3 out of 16 patients (18.8 %) in the Elizaria group.

Also, in both groups, comparable reductions were achieved during the course of therapy in the levels of type II + III PNH erythrocyte and granulocyte clones relative to the initial screening value.

The mean change in the total score of the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) at the end of the treatment period relative to the baseline level at screening was positive in two treatment groups and amounted to 8.1 ± 8.7 (95 % CI [3.4; 12.7]) in the Elizaria group and 2.4 ± 7.0 (95 % CI [-1.3; 6.1]) in the Soliris group ($p > 0.05$). Also, there were no statistically significant differences in the change in the total score of the questionnaire on the quality of life of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30).

Elizaria demonstrated a safety profile similar to that of Soliris. During the study, 13 adverse reactions (ARs) were reported after the administration of the investigational or reference product and they were associated with investigations, blood and lymphatic system disorders, infectious and infestations, renal and urinary disorders, general disorders and administration site conditions, metabolism and nutrition disorders. The proportion of patients with ARs in both treatment groups was similar.

According to the immunogenicity analysis, no statistically significant differences between the groups in terms of ADA detection frequency were identified ($p > 0.05$). ADAs which were identified in two patients developed as a result of previous therapy with Soliris. During the study, new cases of ADA formation were not revealed.

Pediatric patients

The efficacy and safety of eculizumab therapy in the pediatric population with PNH were evaluated in the clinical study in seven patients aged 11 to 17 years. Treatment with eculizumab for 12 weeks in accordance with the recommended dosage regimen was accompanied by a decrease in intravascular hemolysis measured by LDH level. A significant reduction in the number or permanent discontinuation of blood transfusions and improvement in the patients' performance status have been noted as well. The efficacy of eculizumab in this study was comparable with the results obtained in the eculizumab study in adult patients.

The efficacy and safety of eculizumab therapy in the pediatric population with aHUS were evaluated in 37 patients aged 2 months to 18 years. In general, the results in this group of patients are comparable with the study results in the adult population. During the eculizumab therapy, an increase in the platelet count was observed after 26 weeks of treatment, and renal

function control was achieved, which is suggestive of decreased activity of complement-mediated thrombotic microangiopathy.

5.2. Pharmacokinetic properties

Absorption and distribution

In a comparative study of pharmacokinetics in healthy volunteers after a single intravenous injection at a dose of 600 mg, the following values of pharmacokinetic (PK) parameters were obtained (mean values are indicated without correction for body weight): in the Elizaria group: AUC_{0-t} of 15,465.9 μg×h/mL; C_{max} of 158.97 μg/mL; C_{max}/AUC_{0-t} of 0.0115; $T_{1/2}$ of 81.90 h; MRT of 115.26 h; V_d of 4.24 L, and Cl of 40.97 mL/h; in the Soliris group: AUC_{0-t} of 14,058.4 μg×h/mL; C_{max} of 163.50 μg/mL; C_{max}/AUC_{0-t} of 0.0120; $T_{1/2}$ of 65.79 h; MRT of 93.14 h; V_d of 3.93 L, and Cl of 42.98 mL/h.

Biotransformation

Human antibodies undergo endocytosis in the cells of the reticuloendothelial system, where they are catalyzed by lysosomal enzymes to small peptides and amino acids. Eculizumab contains only naturally occurring amino acids and has no known active metabolites.

Elimination

No special studies to assess the eculizumab elimination pathways have been conducted. Eculizumab is not excreted unchanged by the intact kidneys due to its high molecular weight (148 kDa).

In healthy volunteers in a comparative study, mean clearance of eculizumab was 3.03 mL/h/kg for Elizaria and 3.08 mL/h/kg for Soliris; mean distribution volume was 304.87 mL/kg and 282.11 mL/kg, respectively. In patients with PNH, mean clearance according to the reference product amounts to 0.31 ± 0.12 mL/h/kg; mean distribution volume is 110.3 ± 17.9 mL/kg and mean elimination half-life is 11.3 ± 3.4 days. Based on these data, the steady state is achieved within 49–56 days.

In patients with PNH, there was a direct relationship between pharmacodynamic activity of eculizumab and its plasma concentration. In cases where plasma concentration of eculizumab was maintained at the level of ≥35 μg/mL, nearly complete blocking of hemolytic activity was observed in most patients.

In patients with aHUS and the body weight of 70 kg, mean clearance amounts to 0.0139 L/h, and the distribution volume is 5.6 L. The elimination half-life amounts to 297 hours (approximately 12.4 days).

The PK and PD of eculizumab in patients with PNH were studied in a comparative study of the efficacy and safety of Elizaria and Soliris. There were no statistically significant differences either in eculizumab concentration or terminal complement complex concentration between the two treatment groups at all studied time points. In both study groups, the mean eculizumab concentrations before the administration of the next dose of the investigated or reference product and before and after establishing a steady state, exceeded 35 μg/mL, the minimum concentration sufficient to completely inhibit intravascular hemolysis in patients with PNH. After establishing a steady state, the mean eculizumab concentration before the next

administration of the investigated or reference product was 92.16 ± 38.59 μg/mL in the Elizaria group and 133.21 ± 71.56 μg/mL in the Soliris group ($p > 0.05$). The mean clearance value during the period of establishing a steady state in the Elizaria and Soliris groups was 11.70 ± 6.14 mL/h and 8.50 ± 3.56 mL/h, the apparent volume of distribution was 3.80 ± 1.23 L and 3.29 ± 1.19 L, respectively. The mean elimination half-life is 375.08 ± 598.62 h (approximately 15 days) for Elizaria and 277.00 ± 83.75 h (approximately 12 days) for Soliris. All differences are statistically non-significant ($p > 0.05$). In both groups, significant variability of the PK parameters was noted.

Parameters of eculizumab clearance and elimination half-life were studied in patients receiving exchange plasma transfusions. This procedure leads to a decrease in the eculizumab concentration by approximately 50 % within 1 h of transfusion, and the elimination half-life decreases to 1.3 h. Thus, in patients with aHUS receiving plasma transfusions or plasma exchange transfusions, an additional dose of Elizaria is required.

The pharmacokinetic parameters observed in the refractory GMG and NMOSD populations are consistent with those observed in the PNH and aHUS populations.

There is a correlation between the pharmacodynamic activity, measured by the concentration of free C5 < 0.5 μg/mL, and almost complete blocking of terminal complement activity in patients with PNH, aHUS, refractory GMG, and NMOSD.

No studies of the pharmacokinetics of eculizumab in special populations of patients with PNH, refractory GMG, or NMOSD based on gender, race, age (elderly patients), or functional activity of the liver or kidneys have been conducted. The population analysis of the pharmacokinetic data from studies in patients with PNH, aHUS, refractory GMG, and NMOSD has shown that gender, race, elderly age, or the presence of hepatic or renal failure do not affect the pharmacokinetic parameters of eculizumab.

Pediatric patients

The pharmacokinetics of eculizumab in the pediatric population was evaluated in the clinical study in 7 patients with PNH aged 11 to 18 years. In recommended dosing regimen, depending on the body weight, the minimal clearance of eculizumab was 0.0105 L/h. The principles of dosing of eculizumab in children with a body weight below 40 kg were developed based on the data on patients with aHUS.

The data on the relationship between the body weight and clearance and distribution volume were obtained during studies of PK parameters in the pediatric population of patients with aHUS. Thus, the clearance amounted to 10.4, 5.3 and 2.2 mL/h, and the distribution volume was 5.23, 2.76 and 1.21 L for the body weight of 70, 30 and 10 kg, respectively. The elimination half-life is within the range of 349 to 378 hours (approximately 14.5–15.8 days).

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients.

Sodium phosphate monobasic monohydrate,

sodium phosphate dibasic heptahydrate,

sodium chloride,

polysorbate 80,

water for injections.

6.2. Incompatibility.

Due to the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3. Shelf life (period of storage)

2 years and 6 months.

6.4. Special precautions for storage

Store in a dark place at a temperature of 2 to 8 °C. Do not freeze.

6.5. Nature and contents of primary packaging

30 mL of the concentrate in a vial made of hydrolytic class 1 glass, closed with a rubber stopper and sealed with an aluminum-plastic flip-off cap.

1 vial of concentrate with a patient information leaflet is placed into a carton box. The carton flaps are sealed with tamper-evident self-adhesive labels.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Recommendations for solution preparation and infusion technique:

Do not mix Elizaria with another medicinal product in the same syringe or vial when administered intravenously.

Using a sterile syringe with a needle (not included), draw up all the contents of the vial/vials of Elizaria and transfer the recommended dose to the vial with one of the following solutions for injection: 0.9 % sodium chloride solution, 0.45 % sodium chloride solution or 5 % dextrose (glucose) solution to obtain an infusion solution with a concentration of 5.0 mg/mL.

The volume of the prepared solution for infusion containing 5.0 mg of Eculizumab per 1 mL should be: 60 mL (for a dose of 300 mg), 120 mL (for a dose of 600 mg), 180 mL (for a dose of 900 mg) and 240 mL (for a dose of 1,200 mg).

The prepared solution for infusion should be clear and colorless. If the solution is colored or there are inclusions in it, its use is not allowed.

Immediately before the injection, it is necessary to gently shake the vial with the solution for infusion to homogenize the contents of the vial. The temperature of the solution for infusion should be 20 – 25 °C.

The solution for infusion should be used immediately after preparation.

If the infusion is postponed for any reason, it is allowed to store the prepared infusion solution at a temperature of 2 to 8 °C for not more than 24 hours without freezing. Once the said period (24 h) is over, the unused solution must be discarded.

All remaining medicinal product should be destroyed, and the used consumables should be disposed of in the prescribed manner.

7. MARKETING AUTHORIZATION HOLDER

Russian Federation, LLC “Generium-Next”,
14 Constructor Lukin street, Bldg. 12, Floor 6, Room 34, Zelenograd, inter-city area of Silino municipal district, Moscow, 124460, tel.: +7 (495) 988-47-95.

7.1. Representative of the Marketing Authorization Holder

Consumer complaints should be sent to:

Russian Federation, JSC «GENERIUM», Building 273, Zavodskaya street, Volginsky settlement, Petushinsky district, Vladimir region, 601125, tel.: +7 (49243) 72-5-20, 72-5-14.

Contact details of authorized organizations of all EAEU member states to accept consumer complaints are presented below:

Russian Federation
Federal Service for Surveillance in Healthcare
(Roszdravnadzor)
http://roszdravnadzor.ru

8. NUMBER OF THE MARKETING AUTHORIZATION CERTIFICATE

ЛП-No.(000140)-(РГ-RU)

9. DATE OF PRIMARY AUTHORIZATION (CONFIRMATION, RENEWAL OF AUTHORIZATION)

Date of first authorization: February 18, 2021

10. DATE OF TEXT REVISION

The Summary of Product Characteristics of Elizaria is available on the official website of the competent authority of the Eurasian Union member state of the www.rosminzdrav.ru and/or on the information portal of the Eurasian Economic Union at https://eec.eaeunion.org.

*/Stamp: Ministry of Health of the Russian Federation * Federal State Budgetary Institution * Scientific Center for Expert Evaluation of Medicinal Products * EXPERT REPORT IS VALID FOR THIS DOCUMENT VERSION * 0000000009/*

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