ELIZARIA® (ECULIZUMAB)

PHYSICIAN'S GUIDE

Important Information on Serious Adverse Events (Reactions)

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The objective of this Guide is to provide healthcare professionals with information about prevention, identification, monitoring, and/or due management of specific eculizumab-related safety concerns.

ELIZARIA®

ELIZARIA® (INN: eculizumab) is a recombinant humanized monoclonal antibody that binds the C5 complement component.

Eculizumab inhibits the activity of the human terminal complement complex due to high affinity to complement component C5; thus, C5 cleavage to C5a and C5b and the formation of the terminal complement complex C5b-9 are completely inhibited. Eculizumab does not affect the early components of complement activation that are essential for opsonization of microorganisms, initiation of immune responses (both humoral and cell-mediated), and clearance of immune complexes.

ELIZARIA®: INDICATIONS FOR USE

ELIZARIA® (eculizumab) is indicated for the treatment of adult and pediatric patients with:

- Paroxysmal nocturnal hemoglobinuria (PNH). The product efficacy has been confirmed in patients with hemolysis and concomitant clinical symptoms indicative of high disease activity irrespective of the history of blood transfusion.
- Atypical hemolytic uremic syndrome (aHUS).
- Generalized myasthenia gravis (gMG) in patients aged 6 and above who are anti-acetylcholine receptor (AChR) antibody-positive.

ELIZARIA® (eculizumab) is indicated for the treatment of adult patients with:

- Neuromyelitis optica spectrum disorders (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive, with a relapsing course of the disease.

IMPORTANT SAFETY INFORMATION

Risk of serious infection and sepsis

ELIZARIA® mode of action increases the risk of serious infections, specifically meningococcal infection induced by *Neisseria meningitidis* and meningococcal sepsis.

To minimize the risk of infections and their adverse outcomes, the following actions are required:

Meningococcal infection: vaccination and antibacterial prophylaxis

- Vaccinate your patients against meningococcal infection at least 2 weeks before initiating ELIZARIA® if the risk of delayed ELIZARIA® initiation does not exceed the risk of meningococcal infection.
- Vaccines against serotypes A, C, Y, W135, and B (if available) are recommended.
- Vaccination should be performed in accordance with the current national immunization guidelines.
- In some cases, vaccination does not provide for sufficient protection. Keep yourself up to date on the official guidelines for good use of antibiotic treatment.
- All patients should be monitored for early signs of meningococcal infection, undergo appropriate tests immediately if the infection is suspected and, if required, relevant

antibiotics should be prescribed.

- Adult and pediatric patients with contraindications against meningococcal vaccination, and patients receiving ELIZARIA® less than 2 weeks after vaccination should receive antibacterial prophylaxis until 2 weeks after the vaccine dose elapsed or over the entire treatment period if they have not been vaccinated.
- **gMG patients**: certain antibacterial agents may cause the emergence or aggravation of the disease symptoms in gMG patients. If such agents are used, their potential of affecting clinical manifestations of gMG should be reconfirmed, and these manifestations should be closely monitored.

Haemophilus influenzae and pneumococcal infection in pediatric patients: vaccination

PNH and aHUS patients: vaccinate patients under 18 years of age against *Haemophilus influenzae* and pneumococcal infections in strict compliance with the national immunization guidelines for each respective age group at least 2 weeks before initiating ELIZARIA®.

Effect of vaccination on the underlying disease course

Vaccination may further activate the complement. As a result, patients with complement-mediated diseases, including PNH, aHUS, gMG, and NMOSD, may experience intensified signs and symptoms of their underlying disease, such as hemolysis (PNH patients), TMA (aHUS patients), exacerbating gMG or relapsing NMOSD. Therefore, patients should be closely monitored for the disease symptoms after the vaccination.

SIGNS AND SYMPTOMS OF SERIOUS INFECTION

Meningococcal infection

- **Sepsis** is a common manifestation of meningococcal infection in patients receiving eculizumab.
- **Monitor** all patients for early signs of meningococcal infection.
- **Perform appropriate tests immediately** if the infection is suspected and, is required, prescribe relevant antibiotics.
- **Provide the patients receiving eculizumab with the *Patient/Caregiver's Guide*. Explain to them the Guide contents** to boost their awareness of potential serious infections and their relevant signs and symptoms including:

- Headache with nausea or vomiting
- Headache combined with a stiff neck or back
- Headache and fever
- Fever
- Fever and rash
- Fever with fast heart rate
- Confusion
- Severe muscle ache combined with flu-like symptoms
- Sensitivity to light

Young children may additionally present with signs and symptoms as follows: • Rapid breathing • Cold hands and feet • Refusing food and/or vomiting • Unusual cry or moaning • Dislikes being handled • Drowsy, floppy, unresponsive	**Older children** may additionally present with signs and symptoms as follows: • Stiff neck • Drowsy, difficult to wake • Irritability • Uncontrollable shaking and leg pain

- **Provide your patients receiving eculizumab with the *Patient Safety Card*** and explain that they are required to always carry it throughout the treatment period and for 3 months after the last dose of the product and present it to all healthcare professionals they turn for help/advice.
- Discuss the benefits and risks of eculizumab with the patients/parents or patients' personal representatives.
- **Instruct the patients to urgently consult a physician in case of any suspected infection.**

Make sure that the parents/personal representatives of neonates and infants are confident in identifying specific symptoms of headache, fever, and stiff neck. Teach them that infants should also be watched for other symptoms, including inactivity, irritability, vomiting, and loss of appetite, with a particular focus on the necessity to ungently seek medical advice in case of any suspected infection.

Other systemic infections

***Neisseria* infections**

Given ELIZARIA® mode of action, caution should be exercised in the treatment of patients with unresolved systemic infections (specifically those induced by *Neisseria* spp. and encapsulated bacteria). Serious infections induced by *Neisseria* ssp. (besides *Neisseria meningitidis*), including common gonococcal infections, have been reported.

Brief your patients about gonorrhea prevention options based on general recommendations for the prevention of sexually transmitted infections, including the use of barrier protection (contraceptives) in sexually active patients.

Aspergillosis

Aspergillosis cases, some of them lethal, have been reported for patients receiving eculizumab.

The risk factors should be considered such as long-term steroid use, taking immunosuppressive agents, severe pancytopenia, exposure to construction or demolition sites, and pre-existing lung impairment or aspergillosis. If one of the above risk factors is identified before initiating eculizumab, appropriate measures to mitigate the risk of aspergillosis are advisable.

OTHER SERIOUS ADVERSE REACTIONS

Infusion-related reactions, including anaphylaxis

Intravenous ELIZARIA® as well as other intravenous protein drugs may induce infusion-related reactions or may be accompanied by hypersensitivity reactions, including anaphylaxis.

After the product infusion is complete, patients should be followed up for 1 hour. If adverse reactions emerge during the product administration, the infusion rate may be reduced or the infusion should be discontinued, at the physician's discretion. When reducing the infusion rate, ELIZARIA® infusion duration may not exceed 2 hours in adults and pediatric patients, ages 12–18 years, and 4 hours in children under 12 years of age.

Immunogenicity

Rare anti-drug antibody formation cases have been documented during clinical trials in patients receiving eculizumab. No relation between the antibody presence and clinical response or adverse drug reactions has been identified.

ELIZARIA® DISCONTINUATION ASSOCIATED RISKS

Serious intravascular hemolysis in PNH patients

PNH patients initiating ELIZARIA® should continue taking the product if they are getting better.

Patients who discontinued ELIZARIA® should be monitored for intravascular hemolysis intensity for at least 8 weeks. The signs of serious hemolysis include serum LDH levels at least 1.5-fold higher than the upper limit of normal concomitantly with one of the following parameters: >25 % reduction in the PNH cell population (in the absence of the dilution effect in case of blood transfusion) over one week or earlier; hemoglobin concentration less than 50 g/L or its reduction by more than 40 g/L over one week or earlier; the emergence or aggravation of angina pectoris; mental disorders; blood creatinine levels elevated by 50 % or thrombosis.

In case of signs of serious hemolysis after therapy discontinuation, it is recommended that blood (red blood cell mass) transfusion or exchange blood transfusion be performed if, according to flow cytometry data, the PNH cell population is >50 % of the total red blood cell count, and that anticoagulants, corticosteroids be prescribed or ELIZARIA® be rechallenged.

Thrombotic microangiopathy in aHUS patients

After eculizumab was discontinued, the recurrence of TMA symptoms was observed in individual aHUS patients 4 to 127 weeks after the product discontinuation. Life-long treatment with ELIZARIA® is recommended unless there are medical indications for treatment discontinuation.

aHUS patients who discontinued eculizumab should be monitored for the signs and symptoms of severe TMA complications. Monitoring may be insufficient to predict or prevent severe TMA in aHUS patients after the product discontinuation.

TMA manifestations after eculizumab discontinuation include: (1) any two or recurrent changes in one of the following parameters: platelet count reduced by ≤25 % compared to the baseline or maximum platelet count during eculizumab treatment; serum creatinine level elevated by ≥25 % compared to the baseline or minimum level during eculizumab therapy; or serum LDH level elevated by ≥25 % compared to the baseline or minimum level during eculizumab therapy; or (2) any of the following symptoms: mental changes, seizures, angina pectoris, shortness of breath, and thrombosis.

If severe TMA complications emerge after eculizumab discontinuation, it is recommended that eculizumab be rechallenged, and maintenance therapy using plasmapheresis or exchange plasma transfusions or appropriate specific maintenance therapy including hemodialysis, artificial ventilation, or anticoagulant therapy be prescribed.

Worsening course in gMG patients

Eculizumab has been used in gMG patients in the long-term therapy setting only. Patients who discontinued eculizumab should be closely monitored to timely detect the signs and symptoms of deterioration of their condition.

Worsening course in NMOSD patients

Eculizumab has been assessed in NMOSD patients in the long-term therapy setting only, and the product withdrawal effect has not been described yet. Patients who discontinued eculizumab should be closely monitored to timely detect the signs and symptoms of worsening NMOSD.

REPORTING ADVERSE DRUG REACTIONS

It is important that adverse reactions to an authorized drug be reported. This provides for continuous monitoring of the product's benefit–risk balance. Healthcare professionals are required to report any suspected adverse reactions.

One can also report any ELIZARIA®-related adverse reactions to GENERIUM JSC by emailing at **pv@generium.ru** or calling at **+7 (495) 988-47-94** (Russia).

INFORMATION SOURCES

1. Summary of Product Characteristics: Elizaria®, LP-No.(000140)-(RG-RU) of 06.08.2024.
2. Package Leaflet: Information for the Patient – Elizaria®. State Registry of Medicinal Products, LP-No.(000140)-(RG-RU) of 06.08.2024.
3. SOLIRIS® (eculizumab). Healthcare Provider Safety Brochure. Information for healthcare providers who will prescribe or dispense ULTOMIRIS® and SOLIRIS®. Approved 03/2024.
4. Резолюция междисциплинарного совета по профилактике тяжелых инфекций у пациентов с генетическими нарушениями регуляции системы комплемента, получающих терапию экулизумабом. *Эпидемиология и Вакцинопрофилактика*. 2017; 92(1): 51-54 (Resolution of the Interdisciplinary Council on the prevention of severe infections in patients with genetic dysregulation of the complement system receiving eculizumab. *Epidemiology and Vaccinal Prevention.* 2017; 92(1): 51-54).

GENERIUM JSC

Registered office address: Building 273,
Zavodskaya St., Volginsky Village,
Petushinsky District, Vladimir Region
601125 Russian Federation
Phone/fax: +7 (49243) 7 25 20
Moscow Office: 10 Testovskaya St.,
entrance 2, Moscow
123112 Russian Federation
Phone/fax: +7 (495) 988 47 94
info@generium.ru / **www.generium.ru**

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