Sample Appeal Letter for SOLIRIS® (eculizumab)

for Paroxysmal Nocturnal Hemoglobinuria (PNH)

INDICATION

SOLIRIS is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.[1]

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

SOLIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1)*]. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of SOLIRIS, unless the risks of delaying SOLIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. *See Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving SOLIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.**

Because of the risk of serious meningococcal infections, SOLIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [*see Warnings and Precautions (5.2)*].

Please see Important Safety Information on pages 1 and 12 and full Prescribing Information for SOLIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

SOLIRIS®
(eculizumab)
Injection for Intravenous Use
300 mg/30 mL vial

US/SOL-P/0104 V2 06/2024

Introduction

When a payer (health plan or pharmacy benefit manager [PBM]) denies a prior authorization (PA), precertification, or reauthorization request for SOLIRIS prescribed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), your patient has the right to appeal the decision. If your patient wishes to appeal, you and your staff may assist by submitting an appeal letter and supporting documentation.

As part of the appeals process, payers may request additional documentation from you to support coverage of SOLIRIS when approval for its use has been denied. Your letter should explain why SOLIRIS is medically necessary for the specific patient and may include supporting documentation. The letter may be submitted in response to the denial letter or a payer's request for additional documentation. The letter should include patient-specific information, address the reason for denial, be presented on the prescriber's letterhead, and be signed by the prescriber. The provided sample appeal letter gives you a framework for composing an appeal.

This sample appeal letter is provided for informational purposes only and is not legal advice or official guidance from payers. It is not intended to increase or maximize reimbursement by any payer. Alexion does not warrant, promise, guarantee, or make any statement that the use of this information will result in coverage or payment for SOLIRIS or that any payment received will cover providers' costs.

General Tips for Completing an Appeal Letter

Understand the appeals process for the specific payer. It's important to follow the payer's guidelines when submitting an appeal. Payers may have their own appeal request forms, which are usually available on their website. If a form is required, include it with your own letter. Be sure to contact the payer with any questions and obtain written instructions for their appeals process.

When submitting an appeal, timing is critical. Refer to the denial letter to find the timelines for submitting the appeal and any payer-specific guidelines.

In cases of medical urgency, your patient may request an expedited review and can expect to receive a decision within 72 hours. For more information, please visit HealthCare.gov.

Understand the reason for denial. It's important to read the denial letter carefully to understand the reason(s) provided. You may also call the payer to discuss a denial with them; this may help inform you about ways to resolve it in a timely manner.

- **If the denial is due to inaccurate or incomplete information,** carefully review the PA or reauthorization request that you submitted to identify information that is incorrect or was omitted. Resubmit the PA or reauthorization request when all the required information is accurate and complete.
- **If there is a medical reason for the denial,** ensure that your appeal letter includes specific and relevant medical information to support SOLIRIS use according to the payer's criteria. Your letter should clearly explain why you believe SOLIRIS is the most appropriate option for this patient.

Provide all supporting documentation at the same time and in the requested order, as shown in the individual payer's appeal instructions. This might include:

- The payer's appeal form (if required)
- Your appeal letter
- A copy of the payer's denial letter
- Supporting documentation, such as clinical notes, lab results, etc

For more information on the overall appeals process, please refer to the **Alexion SOLIRIS Access and Reimbursement Guide.**

Our dedicated Field Reimbursement Managers (FRMs) can work with you. In the event of a PA denial, FRMs can provide you or your office staff with educational support and guidance. FRMs can help with:

- Payer options for PA resubmission, including details about the resubmission process, peer-to-peer review, appeals process, and associated timelines
- Review of the redacted denial letter or Explanation of Benefits (EOB) letter to provide specific guidance on next steps and best practices

Please see Important Safety Information on pages 1 and 12 and full Prescribing Information for SOLIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

SOLIRIS® (eculizumab) Injection for Intravenous Use 300 mg/30 mL vial

US/SOL-P/0104 V2 06/2024

[John Doe, MD]
[Address]
[City, State, ZIP Code]
[(888) 555-5555]

SAMPLE ONLY
Please copy onto your letterhead.

[Date]
[Contact Name] [Title]
[Name of Health Insurance Plan or PBM]
[Address]
[City, State, ZIP Code]

Re: [First/Second]-Level Appeal for Coverage Denial of SOLIRIS® (eculizumab)
[Request for Expedited Review Due to Medical Urgency]

Denial Letter Date: [MM/DD/YYYY]
Denial Reference #: [Denial Reference #]

Patient: [Name]
Date of Birth: [MM/DD/YYYY]
Member ID Number: [Insurance ID Number] Group Number: [Insurance Group Number]
Rx Bin: [Rx Bin Number] Rx PCN: [Rx PCN Number] Rx Group: [Rx Group Number]

Dear [Contact Name],

I am writing to appeal the coverage denial for [Name of patient]'s treatment with SOLIRIS® (eculizumab) for paroxysmal nocturnal hemoglobinuria (PNH). In the letter referenced above, you stated that the reason for denial was [insert reason for denial: eg, a requirement of a history of trial/failure of, contraindication, or intolerance to pegcetacoplan or iptacopan therapy, lack of transfusion history, low thromboembolic risk]. This letter provides information about my patient's medical history and my treatment rationale.

1 REASON(S) FOR DENIAL AND TREATMENT RATIONALE

[In the appeal letter, you will need to address every denial reason(s) stated in the denial letter from the insurance plan. Provide a clear rationale and explain why you disagree with the denial reason. Refer to "Treatment Rationale to Support Appeal" on pages 6-9.

If applicable, describe your patient's treatment goals and your rationale as to why a step therapy through pegcetacoplan or iptacopan is not optimal for meeting these goals. Clearly explain why you have concerns regarding the requirement that your patient must have a history of trial/ failure of, contraindication, or intolerance to pegcetacoplan or iptacopan. Refer to "Treatment Rationale to Support Appeal" on pages 6-9].

In my medical opinion, SOLIRIS remains the most appropriate treatment for [Name of patient]. The stated reason(s) for denial was [insert each denial reason and address each reason point by point, referring to "Treatment Rationale to Support Appeal" and "Attachments and Supporting Documentation" on pages 6-11; provide any laboratory results if applicable].

2 SUMMARY AND OPTIONAL MEDICAL HISTORY

[After addressing each stated reason for denial, you may wish to summarize your appeal and restate your patient's relevant medical history and laboratory results.]

As stated in my initial authorization request, [Name of patient] is currently [treatment-naïve or stable on the current SOLIRIS regimen].

Based on my assessment of their current clinical symptoms and labs, they require [insert recommendation for addressing patient's current therapeutic needs (eg, effective long-term control of the PNH drastic manifestations including: acute resolution of hemolytic crisis or thrombotic symptoms, terminal complement inhibition to reduce risks of intravascular hemolysis, maintenance of stable regimen, and reduction in barriers to adherence)] for which SOLIRIS treatment is medically necessary.

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[John Doe, MD]
[Address]
[City, State, ZIP Code]
[(888) 555-5555]

SAMPLE ONLY
Please copy onto your letterhead.

[Note: Payer policies may require physician attestation regarding the discussion of alternative treatment options and shared decision-making of a PNH treatment plan with patients previously or currently treated with SOLIRIS. To fulfill these requirements for continued use of SOLIRIS, the following text must be included in the appeal.]

I have counseled the patient on alternative chronic treatment options with PNH. My patient is involved in the decision-making process regarding their PNH therapy plan. Collectively, we have determined that SOLIRIS is the most clinically appropriate treatment choice for managing their PNH at this time.

For the above reasons, I request that you reverse the coverage determination.

3 For your additional information, I am enclosing [list enclosures, such as a copy of the denial letter, supporting clinical documentation, etc]. If you have any further questions, please feel free to call me at [physician's telephone number] to discuss.

Thank you in advance for your immediate attention to this request.

Sincerely,

[Physician's Name], MD
[Physician's Identification Number]
[Physician's Practice Name]
[Physician's Phone Number]
[Physician's Fax Number]
[Physician's Email]

Enclosures
[At the bottom of your letter, list the items you have enclosed. Be sure to include every article that you referenced or any new documentation.]

US/SOL-P/0104 V2 06/2024

1 Treatment Rationale to Support Appeal

In your appeal letter, you may choose to include some of the reasons below for justification. Be sure to attach the supporting references and any additional documentation in your reply.

- **Denial due to indication:** SOLIRIS® (eculizumab) is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).[1]
- **Denial due to meningococcal vaccinations:** Provide documentation of initial series and/or most recent booster(s) for MenACWY, MenABCWY, and MenB vaccinations. If vaccinations are pending approval of therapy, please include a scheduled date for the patient to receive vaccinations.
- **Denial due to transfusion history:** Provide documentation of the history of red blood cell/white blood cell transfusions [number of infusions, dates, as well as the units transfused].
- **Denial due to patient not meeting thrombotic risk [no clot or clone size is too small, no thrombotic event]:** Provide documentation of the history of thromboembolic events and symptoms of thrombosis [neurologic symptoms, abdominal pain, leg swelling], laboratory or imaging results confirming the diagnosis [elevated D-dimer, MRI, CT, and/or PNH clone size (indicative of risk for thromboembolic events)].
- **Denial due to omission of necessary lab results:** Provide any appropriate or confirmatory lab values [evidence of LDH level ≥1.5 times the upper limit of normal, abnormal high sensitivity flow cytometry results, negative direct antiglobulin or Coombs' test, elevated reticulocytes, decreased levels of hemoglobin, or decreased levels of serum haptoglobin].
- **Denial due to required use of pegcetacoplan:** In my medical opinion, pegcetacoplan is not an appropriate step for my patient based on the following relevant clinical criteria [below is a list of potential considerations why pegcetacoplan may not be appropriate for your patient given their case or specific clinical presentation. One or more of these reasons may apply to your patient's individual case].
    - **Patient requires acute treatment for hemolytic crisis or thrombotic symptoms.**
      [Name of patient] is currently experiencing [an acute hemolytic crisis or acute thrombotic symptoms] based on [insert laboratory and clinical data supporting diagnosis (eg, predisposing patient factors, platelet counts indicative of severe thrombocytopenia, elevated D-dimer, and/or history of prior deep vein thrombosis)].[2,3] According to the prescribing information, it took four to six weeks for pegcetacoplan to achieve steady-state serum concentrations following the first dose.[4] In my medical opinion, pegcetacoplan will not mitigate this acute crisis.
    - **Patient is complement inhibitor-naïve and their flow cytometry results show a clone size of 5%-9%.**
      [Name of patient] has a diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size 5%-9%. In my medical opinion, pegcetacoplan is not an appropriate step for my patient as they would not have been included in the PRINCE study (complement inhibitor–naïve trial).[5]
    - **Health risk in performing or adhering to self-injection due to physical and/or cognitive impairment.**
      In my opinion [Name of patient] is unlikely to be able to perform the steps necessary to regularly self-administer pegcetacoplan given [insert complicating factors that may contribute to nonadherence to pegcetacoplan (physical and mental impairments, reduced functional capacity, lack of psychosocial or caregiver support, patient lifestyle)]. Pegcetacoplan administration requires patients to self-administer twice weekly subcutaneous infusions via an infusion pump.[4] Given this route of administration, I do not believe that [Name of patient] can successfully adhere to this treatment regimen.

1 Treatment Rationale to Support Appeal (cont.)

- **Denial due to required use of iptacopan:** In my medical opinion, iptacopan is not an appropriate step for my patient based on the following relevant clinical criteria [below is a list of potential considerations why iptacopan may not be appropriate for your patient given their case or specific clinical presentation. One or more of these reasons may apply to your patient's individual case].
  - **Patient has a lipid disorder and/or a history of a lipid disorder.**
    Iptacopan increases total cholesterol, LDL cholesterol, and serum triglycerides, and some patients required cholesterol-lowering medications throughout the iptacopan clinical trials. Further, in the APPLY-PNH clinical trial for iptacopan, 6% (4/62) of the patients in the iptacopan group vs 0% in the anti-C5 inhibitor group had a lipid disorder (ie, dyslipidemia, blood cholesterol increased, low-density lipoprotein increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia). In the APPOINT-PNH trial, 8% (3/40) of the patients in the iptacopan group had a lipid disorder.[6]

    In my medical opinion, iptacopan is not an appropriate step for my patient as they [have a lipid disorder/have a past medical history of a lipid disorder] and will require closer monitoring of lipid parameters periodically and may require interventions to treat their lipid disorder during treatment.[6]

    My patient has elevated serum transaminases. Increases in serum transaminases have been reported with patients on lipid-lowering medications. In my medical opinion, iptacopan would not be an appropriate step therapy for my patient because treatment with iptacopan may require my patient to start treatment with a lipid-lowering medication and may further increase my patient's serum transaminase levels.[6-8]
  - **Patient has thrombocytopenia and/or a history of thrombocytopenia.**
    In the APPLY-PNH clinical trial for iptacopan, 6% (4/62) of the patients in the iptacopan group vs 0% in the anti-C5 (SOLIRIS and ULTOMIRIS) group had thrombocytopenia.[6] In my medical opinion, iptacopan is not an appropriate step for [Name of patient] as they currently have laboratory evidence of thrombocytopenia with a platelet count of [insert platelet count] [and/or a past medical history of thrombocytopenia].
  - **Patient is taking a CYP2C8 inducer and/or a CYP2C8 inhibitor.**
    CYP2C8 inducers (eg, rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy of iptacopan.[6] In my medical opinion, iptacopan is not an appropriate step for [Name of patient] as they are currently on a CYP2C8 inducer, [Name of CYP2C8 inducer], and will require additional monitoring for loss of efficacy of iptacopan.[6] Further, if the loss of efficacy of iptacopan becomes evident, the patient may have to go through dose adjustments and/or discontinuation of [Name of CYP2C8 inducer] on which they are currently stable.[6]

    Strong CYP2C8 inhibitors (eg, gemfibrozil) may increase iptacopan exposure, which may result in an increased risk for adverse reactions with iptacopan.[6] Therefore, coadministration of iptacopan with CYP2C8 inhibitors is not recommended.[6] In my medical opinion, iptacopan is not an appropriate step for [Name of patient] as they are currently on a strong CYP2C8 inhibitor, [Name of strong CYP2C8 inhibitor], putting them at risk for increased adverse reactions of iptacopan such as hyperlipidemia.[6]
  - **Iptacopan lacks real-world evidence.**
    As iptacopan was recently approved in 2023, iptacopan lacks real-world evidence.[9] [Name of patient] and I prefer to use a therapy, such as SOLIRIS, that has real-world evidence, 17 years of approved use, and shows substantial and demonstrated established safety and efficacy to patients.[1]

1 Treatment Rationale to Support Appeal (cont.)

- **Health risk in performing or adhering to self-administration of a twice-daily oral dosing regimen due to history of medication nonadherence.**
  In my medical opinion [Name of patient] is unlikely to be able to perform the steps necessary to adhere to iptacopan oral intake given [insert complicating factors that may contribute to nonadherence to iptacopan (history of nonadherence to oral medications, physical and mental impairments, reduced functional capacity, lack of psychosocial or caregiver support, patient lifestyle)]. Iptacopan administration requires patients to self-administer twice-daily oral medications.[6] Given this route of administration, I do not believe that [Name of patient] can successfully adhere to this treatment regimen. Iptacopan has a short half-life (~20 hours) and may not be a good choice for patients who have a history of medication nonadherence. Missed doses, especially in the setting of complement-amplifying conditions such as infections or excessive consumption of alcohol, could lead to massive hemolysis and risk for thrombosis.[2]
- **Patient's flow cytometry results show a clone size of 5%-9%.**
  [Name of patient] has a diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size 5%-9%. In my medical opinion, iptacopan is not an appropriate step for my patient as they would not have been included in the APPLY-PNH or APPOINT-PNH study.[10,11]
- **Patient has laboratory evidence of bone marrow failure.**
  [Name of patient] has laboratory evidence of bone marrow failure (reticulocytes <100x10E9/L; platelets <30x10E9/L; neutrophils <500x10E6/L). In my medical opinion, iptacopan is not an appropriate step for my patient as they would not have been included in the APPLY-PNH or APPOINT-PNH studies.[10,11]

1 Treatment Rationale to Support Appeal (cont.)

PEGASUS Study Design – Select Patient Inclusion Criteria

In my medical opinion, pegcetacoplan is not an appropriate step for my patient as they would not have been included in the PEGASUS phase 3 clinical trial based on the following select relevant study inclusion criteria.[12] [List specific reason(s) based on provided select "PEGASUS Study – Select Patient Inclusion Criteria" below]

- Patients with hemoglobin level <10.5 g/dL despite treatment with stable doses of eculizumab for ≥3 months prior to screening[12]
- Patients were required to have reticulocytes >1.0 × ULN, platelets >50 × 10^9/L, and neutrophils >0.5 × 10^9/L[12]
- Participants were also required to have a body mass index <35.0 kg/m^2 [12]

PRINCE Study Design – Select Patient Inclusion Criteria

In my medical opinion, pegcetacoplan is not an appropriate step for my patient as they would not have been included in the PRINCE phase 3 clinical trial based on the following select relevant study inclusion criteria.[5] [List specific reason(s) based on provided select "PRINCE Study – Select Patient Inclusion Criteria" below]

- Hemoglobin level below the LLN (male: <13.6 g/dL and female: <12.0 g/dL)[5]
- Ferritin levels ≥LLN (≥13 ng/mL) or total iron binding capacity ≤ULN (≤155 µg/dL)[5]
- A body mass index ≤35 kg/m^2, platelets >50,000/mm^3, and absolute neutrophil count >500/mm^3 [5]
- PNH diagnosis confirmed by high-sensitivity flow cytometry (granulocyte or monocyte clone >10%)[5]

APPLY-PNH Study Design – Select Patient Inclusion Criteria

In my medical opinion, iptacopan is not an appropriate step for my patient as they would not have been included in the APPLY-PNH phase 3 clinical trial based on the following select relevant study inclusion criteria.[10] [List specific reason(s) based on provided select "APPLY-PNH Study – Select Patient Inclusion Criteria" below]

- Mean hemoglobin level <10 g/dL[10]
- Diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size ≥10%[10]

APPOINT-PNH Study Design – Select Patient Inclusion Criteria

In my medical opinion, iptacopan is not an appropriate step for my patient as they would not have been included in the APPOINT-PNH phase 3 clinical trial based on the following select relevant study inclusion criteria.[11] [List specific reason(s) based on provided select "APPOINT-PNH Study – Select Patient Inclusion Criteria" below]

- Mean hemoglobin level <10 g/dL[11]
- Diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size ≥10%[11]

Rationale for Reauthorization for Patients Currently Receiving SOLIRIS® (eculizumab)

Health plans often require a prior authorization (PA) for patients receiving specialty medications and orphan drugs treating rare diseases. In many cases, after a patient has received a PA, the patient will need a reauthorization (sometimes known as a renewal authorization) after a specified time period. Obtaining a reauthorization for your patient is often required to confirm that the drug continues to be medically necessary and that the patient has responded to therapy.

- **Denial due to new documentation not previously required:**
  The reauthorization requirements for [Name of patient] have changed since they were initially authorized for treatment with SOLIRIS. [List of additional documentation that is now required] [is/are] now required to obtain reapproval for SOLIRIS. I am requesting a medical exception to continue [Name of patient]'s current treatment based on the original authorization criteria because they have had a demonstrated clinical improvement as evidenced by [insert demonstrated clinical response rationale and/or documentation].

- **Denial due to specific reauthorization clinical improvement criteria:**
  In my medical opinion, [Name of patient] is currently responding positively to treatment with SOLIRIS as evidenced by [list specific measures such as: improvement in hemolysis, decrease in lactate dehydrogenase (LDH), reduced need for red blood cell transfusions, increased or stabilization of hemoglobin levels, fewer thrombotic events].[13,14] Although [Name of patient] may partially meet [list specific denial reason/specified lab result or clinical measure] reauthorization criteria, I believe SOLIRIS is still the optimal therapy for reaching this patient's treatment goals of [controlling IVH, preventing thrombosis, reducing breakthrough hemolysis, decreasing end organ damage].[15-24]

- **Denial due to change in policy required step edit:**
  [Name of patient] was diagnosed with PNH on [date] and has received SOLIRIS treatment since [date of first infusion]. [Name of patient] received authorization for SOLIRIS based on initial PA criteria. [He is/She is/They are] currently responding positively to treatment with SOLIRIS as demonstrated by [increased or stabilization of hemoglobin levels, reduction in transfusions, improvement in hemolysis, decrease in LDH].[13,14] [He is/She is/They are] currently stable on this treatment regimen, and it would be clinically inappropriate to require them to stop treatment with SOLIRIS or switch to another therapy given the risk of [hemolysis, thrombosis, hematologic instability, decline in renal function, pulmonary hypertension, and/or end organ damage].[15-24]

2 Optional Medical History

You may find it helpful to include a brief impactful medical history in your patient's appeal letter with only the most clinically significant facts repeated, such as:

- Lab results confirming a diagnosis of PNH
  - Clinical, imaging, and antibody findings including high-sensitivity flow cytometry confirming PNH with a granulocyte or monocyte clone size ≥5%
  - LDH level ≥1.5 times the upper limit of normal
- Clinical rationale for initiating SOLIRIS® (eculizumab) in this patient
  - History of transfusions
  - Evidence of acute hemolytic crisis or thrombotic symptoms (ie, platelet counts indicative of severe thrombocytopenia, elevated D-dimer, and/or history of prior deep vein thrombosis)
  - Impact of PNH on patient's level of physical function
  - Health risk in performing self-injection due to physical and/or cognitive impairment (ie, physical and mental impairments, reduced functional capacity, and lack of psychosocial or caregiver support)

3 Attachments and Supporting Documentation

In the appeal, you only need to include the original appeal letter and new supporting documentation. If you referred to any specific articles or obtained any photographs or attestations, be sure to attach them to the appeal.

Additional resources that may be used in submitting your letter of appeal may include the SOLIRIS Prescribing Information, the original denial letter, the SOLIRIS Letter of Medical Necessity, and the SOLIRIS Access and Reimbursement Guide.

References: 1. SOLIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **2.** Brodsky RA. Treatment and prognosis of paroxysmal nocturnal hemoglobinuria. UpToDate. Updated November 27, 2023. Accessed January 3, 2024. https://www.uptodate.com/contents/treatment-and-prognosis-of-paroxysmal-nocturnal-hemoglobinuria **3.** Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers*. 2017;3:17028. **4.** EMPAVELI. Prescribing information. Apellis Pharmaceuticals, Inc. **5.** Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. *Blood Adv*. 2023;7(11):2468-2478. **6.** FABHALTA. Prescribing information. Novartis AG. **7.** LIPITOR. Prescribing information. Viatris Inc. **8.** CRESTOR. Prescribing information. Astrazeneca. **9.** US Food and Drug Administration. Department of Health and Human Services. FABHALTA NDA218276 approval letter. December 5, 2023. Accessed December 12, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/218276Orig1s000ltr.pdf **10.** ClinicalTrials.gov identifier: NCT04558918. Accessed November 29, 2023. https://clinicaltrials.gov/study/NCT04558918 **11.** ClinicalTrials.gov identifier: NCT04820530. Accessed November 29, 2023. https://clinicaltrials.gov/study/NCT04820530 **12.** Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;384(11):1028-1037. **13.** Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 2019;133(6):530-539. **14.** Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2019;133(6):540-549. **15.** Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121(25):4985-4996. **16.** De Latour RP, Mary JY, Salanoubat C, et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood*. 2008;112(8):3099-3106. **17.** Loschi M, Porcher R, Barraco F, et al. Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study. *Am J Hematol*. 2016;91(4):366-370. **18.** Hillmen P, Elebute M, Kelly R, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. *Am J Hematol*. 2010;85(8):553-559. **19.** Clark DA, Butler SA, Braren V, Hartman RC, Jenkins DE Jr. The kidneys in paroxysmal nocturnal hemoglobinuria. *Blood*. 1981;57(1):83-89. **20.** Weitz I, Meyers G, Lamy T, et al. Cross-sectional validation study of patient-reported outcomes in patients with paroxysmal nocturnal haemoglobinuria. *Intern Med J*. 2013;43(3):298-307. **21.** Nishimura JI, Kanakura Y, Ware RE, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine*. 2004;83(3):193-207. **22.** Hill A, Rother RP, Wang X, et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2010;149(3):414-425. **23.** Hill A, Sapsford RJ, Scally A, et al. Under-recognized complications in patients with paroxysmal nocturnal haemoglobinuria: raised pulmonary pressure and reduced right ventricular function. *Br J Haematol*. 2012;158(3):409-414. **24.** Jang JH, Kim JS, Yoon SS, et al. Predictive factors of mortality in population of patients with paroxysmal nocturnal hemoglobinuria (PNH): results from a Korean PNH registry. *J Korean Med Sci*. 2016;31(2):214-221.

Please see Important Safety Information on pages 1 and 12 and full Prescribing Information for SOLIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

SOLIRIS® (eculizumab) Injection for Intravenous Use 300 mg/30 mL vial

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SELECT IMPORTANT SAFETY INFORMATION FOR SOLIRIS® (eculizumab) (cont.)

CONTRAINDICATIONS

- SOLIRIS is contraindicated for initiation in patients with unresolved serious *Neisseria meningitidis* infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

SOLIRIS, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with SOLIRIS. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information.

If urgent SOLIRIS therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including SOLIRIS. The benefits and risks of treatment with SOLIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis*.

Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if these signs and symptoms occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of SOLIRIS in patients who are undergoing treatment for serious meningococcal infection, depending on the risks of interrupting treatment in the disease being treated.

ULTOMIRIS and SOLIRIS REMS

Due to the risk of serious meningococcal infections, SOLIRIS is available only through a restricted program called ULTOMIRIS and SOLIRIS REMS.

Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of SOLIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of SOLIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, the signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card with them at all times during and for 3 months following SOLIRIS treatment.

Further information is available at www.UltSolREMS.com or 1-888-765-4747.

Other Infections

Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

SOLIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections with *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. Additionally, *Aspergillus* infections have occurred in immunocompromised and neutropenic patients. Children treated with SOLIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP recommendations. Patients receiving SOLIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

Monitoring Disease Manifestations After SOLIRIS Discontinuation

Monitor patients after discontinuing SOLIRIS for at least 8 weeks to detect hemolysis.

Thrombosis Prevention and Management

The effect of withdrawal of anticoagulant therapy during SOLIRIS treatment has not been established. Therefore, treatment with SOLIRIS should not alter anticoagulant management.

Infusion-Related Reactions

Administration of SOLIRIS may result in infusion-related reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion-related reaction which required discontinuation of SOLIRIS. Interrupt SOLIRIS infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) were: headache, nasopharyngitis, back pain, and nausea.

To report SUSPECTED ADVERSE REACTIONS contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full prescribing information for SOLIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

ALEXION® AstraZeneca Rare Disease

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