

SOLIRIS® (ECULIZUMAB)

Policy Number: PHARMACY 277.9 T2

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Related Policies
<ul style="list-style-type: none"> • Acquired Rare Disease Drug Therapy Exception Process • Experimental/Investigational Treatment • Experimental/Investigational Treatment for NJ Plans • Home Health Care • Maximum Dosage • Specialty Medication Administration - Site of Care Review Guidelines

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	Medical
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes ^{1,3,4}
Precertification with Medical Director Review Required	Yes ^{1,3,4}
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Home, Office, Freestanding Ambulatory Infusion Suite (not associated with a hospital)
Special Considerations	<p>¹Soliris requires precertification with review by a Medical Director or their designee in all sites of service.</p> <p>²New Jersey Small Members should refer to their certificate of coverage for precertification guidelines and quantity limit guidelines.</p> <p>³Requests for hospital outpatient facility infusion of</p>

Special Considerations
(continued)

Soliris require additional precertification, with review by a Medical Director or their designee. Refer to Oxford's [Specialty Medication Administration - Site of Care Review Guidelines](#) policy.

⁴Home infusion of Soliris requires additional precertification for the home care services.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow coverage of experimental/investigational treatments for life-threatening illnesses when certain conditions are met. Members should refer to their member specific benefit plan document for additional information. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the member specific benefit plan document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to Oxford's [Acquired Rare Disease Drug Therapy Exception Process](#) policy.

** Additional Information: Clinical coverage in this policy addresses the drug only. It does not address coverage for drug administration in a hospital outpatient department. Requests for hospital outpatient facility infusion of Soliris require additional precertification with review by a Medical Director or their designee. Refer to the member-specific benefit document and Oxford's [Specialty Medication Administration - Site of Care Review Guidelines](#) policy. The member-specific benefit document determines coverage.

Requests for home infusion of Soliris require additional pre-certification for the home care services. Refer to Oxford's [Home Health Care](#) policy.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Soliris (eculizumab) is proven for the treatment of:

- **Atypical hemolytic uremic syndrome (aHUS)¹**
Soliris is medically necessary when all of the following criteria are met:
 - **Initial Therapy:**
 - Documentation supporting the diagnosis of aHUS by ruling out **both** of the following:
 - Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS)
 - Thrombotic thrombocytopenia purpura (TTP) (e.g., rule out ADAMTS13 deficiency)
 - and**
 - Soliris is initiated and titrated according to the US FDA labeled dosing for aHUS, up to a maximum of 1200 mg every 2 weeks; **and**
 - Prescribed by or in consultation with a hematologist; **and**
 - Initial authorization will be for no more than 6 months.
 - **Continuation Therapy:**
 - Patient has previously been treated with Soliris; **and**
 - Documentation demonstrating a positive clinical response from baseline (e.g., reduction of plasma exchanges, reduction of dialysis, increased platelet count, reduction of hemolysis); **and**
 - Soliris is dosed according to the US FDA labeled dosing for aHUS: 1200 mg every 2 weeks, allowing for dose adjustments due to plasmapheresis, plasma exchange, or fresh frozen plasma infusions; **and**
 - Prescribed by or in consultation with a hematologist; **and**
 - Reauthorization will be for no more than 12 months.

- **Paroxysmal nocturnal hemoglobinuria (PNH)¹**

Soliris is medically necessary when all of the following criteria are met:

- **Initial Therapy:**

- Documentation supporting the diagnosis of PNH with at least **one** of the following criteria:
 - At least 10% PNH type III red cells
 - Greater than 50 % of glycosylphosphatidylinositol-anchored proteins (GPI-AP)-deficient polymorphonuclear cells (PMNs)

and

- **One** of the following:

- Patient is transfusion dependent as defined as **one** of the following:

- Hemoglobin \leq 7 g/dL

- **Both** of the following

- Hemoglobin \leq 9 g/dL

- Patient is experiencing symptoms of anemia

or

- Patient has a documented history of major adverse vascular events from thromboembolism;

and

- Soliris is initiated and titrated according to the US FDA labeled dosing for PNH, up to a maximum of 900 mg every 2 weeks; **and**

- Prescribed by or in consultation with a hematologist; **and**

- Initial authorization will be for no more than 6 months.

- **Continuation Therapy:**

- Patient has previously been treated with Soliris; **and**

- Documentation demonstrating a positive clinical response from baseline (e.g., increased or stabilization of hemoglobin levels, reduction in transfusions, etc.); **and**

- Soliris is dosed according to the US FDA labeled dosing for PNH: 900 mg every 2 weeks; **and**

- Prescribed by or in consultation with a hematologist; **and**

- Reauthorization will be for no more than 12 months.

Generalized myasthenia gravis:^{1,9,11}

Soliris is medically necessary when all of the following criteria are met:

- **Initial Therapy:**

- Submission of medical records (e.g., chart notes, laboratory values, etc.) to support the diagnosis of generalized myasthenia gravis (gMG) by a neurologist or in consultation with a neurologist confirming **all** of the following:

- Patient has not failed a previous course of Soliris therapy; **and**

- Positive serologic test for anti-AChR antibodies; **and**

- **One** of the following:

- History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation

- History of positive anticholinesterase test, e.g. edrophonium chloride test

- Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating neurologist

and

- Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of class II, III, or IV at initiation of therapy; **and**

- Patient has a Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL) total score \geq 6 at initiation of therapy; **and**

- **Both** of the following:

- History of failure of at least **one** immunosuppressive agent over the course of at least 12 months [e.g., azathioprine, methotrexate, cyclosporine, mycophenylate, etc.]; **and**

- b) Patient has required 2 or more courses of plasmapheresis/plasma exchange and/or intravenous immune globulin for at least 12 months without symptom control

and

- Patient is currently on a stable dose (at least 2 months) of immunosuppressive therapy; **and**

- Soliris is initiated and titrated according to the US FDA labeled dosing for gMG, up to a maximum of 1200 mg every 2 weeks; **and**

- Prescribed by or in consultation with a Neurologist; **and**

- Initial authorization will be for no more than 6 months.

- **Continuation Therapy:**

- Patient has previously been treated with Soliris; **and**

- Submission of medical records (e.g., chart notes, laboratory tests) to demonstrate a positive clinical response from baseline as demonstrated by at least **all** of the following:

- Improvement and/or maintenance of at least a 3 point improvement (reduction in score) in the MG-ADL score from pre-treatment baseline.
 - Reduction in signs and symptoms of myasthenia gravis
 - Maintenance, reduction, or discontinuation of dose(s) of baseline immunosuppressive therapy (IST) prior to starting Soliris*.
- ***Note:** Add on, dose escalation of IST, or additional rescue therapy from baseline to treat myasthenia gravis or exacerbation of symptoms while on Soliris therapy will be considered as treatment failure.

and

- Soliris is dosed according to the US FDA labeled dosing for gMG: up to a maximum of 1200 mg every 2 weeks; **and**
- Prescribed by or in consultation with a Neurologist; **and**
- Reauthorization will be for no more than 12 months.

Soliris is unproven and not medically necessary for treatment of Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Soliris (eculizumab) is a complement inhibitor indicated for:¹

- Treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.
- Treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.
- Treatment of adult patients with generalized Myasthenia Gravis (gMG) who are antiacetylcholine receptor (AChR) antibody positive.

Limitations of Use:¹

- Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Use of Soliris is **not recommended** in these situations.

The use of Soliris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early:

- Vaccinate for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies.
- Revaccinate patients in accordance with ACIP recommendations, considering the duration of Soliris therapy.
- Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris.
 - If urgent Soliris therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible.
- Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if an infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at <http://www.solirisrems.com/>.^{1,3}

BACKGROUND

Ecuzumab is a monoclonal antibody that binds with high affinity to complement protein C5, which inhibits its cleavage to C5a and C5b and prevents the generation of the terminal complement complex C5b-9. In those patients with paroxysmal nocturnal hemoglobinuria (PNH), eculizumab inhibits terminal complement mediated intravascular hemolysis. In patients with atypical hemolytic uremic syndrome (aHUS), impairment in the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy. The precise mechanism by which eculizumab exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.¹⁻³

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan

document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
J1300	Injection, eculizumab, 10 mg

ICD-10 Diagnosis Code	Description
D59.3	Hemolytic-uremic syndrome
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
G70.00	Myasthenia gravis without (acute) exacerbation

Maximum Dosage Requirements

Maximum Allowed Quantities by HCPCS Units

This section provides information about the maximum dosage per administration for omalizumab administered by a medical professional.

Medication Name		Diagnosis	Maximum Dosage per Administration	HCPCS Code	Maximum Allowed
Brand	Generic				
Soliris	Eculizumab	aHUS	1200 mg	J1300	120 HCPCS units (10 mg per unit)
Soliris	Eculizumab	Myasthenia Gravis	1200 mg	J1300	120 HCPCS units (10 mg per unit)
Soliris	Eculizumab	PNH	900 mg	J1300	90 HCPCS units (10 mg per unit)

Maximum Allowed Quantities by National Drug Code (NDC) Units

The allowed quantities in this section are calculated based upon both the maximum dosage information supplied within this policy as well as the process by which NDC claims are billed. This list may not be inclusive of all available NDC's for each drug product and is subject to change.

Medication Name		Diagnosis	How Supplied	National Drug Code	Maximum Allowed
Brand	Generic				
Soliris	Eculizumab	aHUS	300 mg vials	25682-0001-01	4 vials/120ml
Soliris	Eculizumab	Myasthenia Gravis	300 mg vials	25682-0001-01	4 vials/120ml
Soliris	Eculizumab	PNH	300 mg vials	25682-0001-01	3 vials/90ml

CLINICAL EVIDENCE

Proven/Medically Necessary

Atypical Hemolytic Uremic Syndrome (aHUS)

Eculizumab is indicated for the treatment of atypical hemolytic uremic syndrome (aHUS).¹

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Eculizumab is indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).¹

Hillmen et al evaluated the long-term safety and efficacy of continuous administration of eculizumab in 195 patients with paroxysmal nocturnal hemoglobinuria (PNH) over 66 months.² Patients previously enrolled in the Phase II pilot study and its extensions, the Phase III TRIUMPH (Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria) study (NCT00122330), or the Phase III SHEPHERD (Safety in Hemolytic PNH Patients Treated With Eculizumab: A Multi-Center Open-Label Research Design) study (NCT00130000) were eligible to participate. All patients had a minimum of 10% PNH red blood cells at enrolment in the parent trials and were vaccinated with a meningococcal vaccine at least 14 days prior to the first eculizumab infusion in the parent studies. Efficacy assessments were performed at least every 2 weeks from the time of initiation of eculizumab therapy in the parent study. Efficacy endpoints included patient survival degree of hemolysis, thrombotic events (TE), mean change from baseline in hemoglobin and the number of units of transfused packed red blood cells (PRBCs) administered. Assessments of renal function were performed over the duration of the study by determining the CKD stage using formulas for estimated glomerular filtration rate (GFR). Safety was assessed through monitoring of adverse events (AEs), clinical laboratory tests and vital signs. Four patient deaths were reported, all unrelated to treatment, resulting in a 3-year survival estimate of 97.6%. All patients showed a reduction in lactate dehydrogenase levels, which was

sustained over the course of treatment (median reduction of 86.9% at 36 months). Incidence of TEs decreased by 81.8%, with 96.4% of patients remaining free of TEs. Researchers observed a time-dependent improvement in renal function: 93.1% of patients exhibited improvement or stabilization in CKD score at 36 months. Transfusion independence increased by 90.0% from baseline, with the number of red blood cell units transfused decreasing by 54.7%. The median treatment duration was 30.3 months with a maximum duration of 66 months. Eculizumab was well tolerated, with no evidence of cumulative toxicity and a decreasing occurrence of adverse events over time. Very few patients discontinued treatment. Researchers concluded that long-term treatment with eculizumab resulted in sustained improvement in patient outcomes by rapidly reducing hemolysis and significantly reducing the frequency of severe and life-threatening morbidities, such as TEs and CKD, and thus, improving patient survival.

Generalized Myasthenia Gravis

Eculizumab is indicated for the treatment of generalized myasthenia gravis.¹

Howard et al completed a phase 3 randomized, double-blind, placebo-controlled, multi-center study (REGAIN) that assessed the efficacy and safety of eculizumab in patients 18 years of age and older, with a confirmed diagnosis of generalized myasthenia gravis.^{9,11} Patients were required to be classified by the Myasthenia Gravis Foundation of America as Class II to IV at screening, and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale ≥ 6 at screening and randomization, and vaccination against *Neisseria meningitidis*. Patients were also to have failed at least two immunosuppressive agents, or failed at least one agent, and require chronic plasma exchange or IVIG for 12 months without symptom control. One hundred twenty-five patients were randomized to receive either placebo (n=63), or eculizumab (n=62): 900 mg IV weekly for 4 doses, followed by 1,200 mg IV every 2 weeks during weeks 4 through 26. Primary outcome measures included the change in total MG-ADL score and the change in MG-ADL total score from baseline at week 26 as compared to placebo. A clinical response in MG-ADL was defined as at least a 3-point improvement. The primary analysis showed no significant difference between eculizumab and placebo. In evaluating clinically meaningful response, a higher proportion of patients achieved a clinically meaningful response with eculizumab than with placebo ($p < 0.05$). No deaths or cases of meningococcal infection occurred during the study. The most common adverse events in both groups were headache and upper respiratory tract infection. Myasthenia gravis exacerbations were reported by six (10%) patients in the eculizumab group and 15 (24%) in the placebo group. Six (10%) patients in the eculizumab group and 12 (19%) in the placebo group required rescue therapy. The change in the MG-ADL score was not statistically significant between eculizumab and placebo, as measured by the worst-rank analysis. Eculizumab was well tolerated. The authors disclosed that the use of a worst-rank analytical approach proved to be an important limitation of this study since the secondary and sensitivity analyses results were inconsistent with the primary endpoint result. The authors state that further research into the role of complement is needed.

Unproven/Not Medically Necessary

Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).¹ While the few studies available demonstrate possible efficacy of eculizumab in treating Shiga toxin E. coli-related hemolytic uremic syndrome,⁴⁻⁶ further studies are warranted to demonstrate that it is both safe and effective for this indication.

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee [2018D0049F]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
08/01/2018	<ul style="list-style-type: none"> • Updated coverage rationale; replaced language indicating “Soliris is proven <i>and/or medically necessary</i> for the treatment of generalized myasthenia gravis when all of the [listed] criteria are met” with “Soliris is proven for the treatment of generalized myasthenia gravis; <i>Soliris is medically necessary</i> when all of the [listed] criteria are met” • Updated supporting information to reflect the most current references • Archived previous policy version PHARMACY 277.8 T2