Clinical Policy: Eculizumab (Soliris)

Reference Number: CP.PHAR.97
Effective Date: 03.01.12
Last Review Date: 02.19
Line of Business: Commercial, Medicaid, HIM-Medical Benefit

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Eculizumab (Soliris®) is a complement inhibitor.

FDA Approved Indication(s)

Soliris is indicated for the treatment of:

- Patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
- Patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy
- Adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive

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

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Soliris is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Paroxysmal Nocturnal Hemoglobinuria (must meet all)**:**

1. Diagnosis of PNH;
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 18 years;
4. Flow cytometry shows ≥ 10% PNH cells;
5. Member has history of one of the following (a or b):
   a. ≥ 1 transfusion in the past 24 months due to documented hemoglobin < 7 g/dL in members without anemia symptoms or < 9 g/dL in members with anemia symptoms;
   b. Thrombosis;
6. Dose does not exceed 600 mg per week for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter.

Approval duration: 6 months

B. Atypical Hemolytic Uremic Syndrome (must meet all)**:**
1. Diagnosis of aHUS (i.e., complement-mediated HUS);
2. Prescribed by or in consultation with a hematologist or nephrologist;
3. Age ≥ 2 months;
4. Dose does not exceed 900 mg per week for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter.

Approval duration: 6 months

C. Generalized Myasthenia Gravis (must meet all)**:**
1. Diagnosis of gMG;
2. Prescribed by or in in consultation with a neurologist;
3. Age ≥ 18 years;
4. Myasthenia Gravis-Activities of Daily Living (MG-ADL) score ≥ 6 at baseline;
5. Myasthenia Gravis Foundation of America Clinical Classification (MGFA) Class II to IV;
6. Member has positive serologic test for anti-AChR antibodies;
7. Failure of a corticosteroid (*see Appendix B*) unless contraindicated or clinically significant adverse effects are experienced;
8. Failure of a cholinesterase inhibitor (*see Appendix B*) unless contraindicated or clinically significant adverse effects are experienced;
9. Failure of two immunosuppressive therapies (*see Appendix B*) unless contraindicated or clinically significant adverse effects are experienced;
10. Dose does not exceed 900 mg per week for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter.

Approval duration: 6 months

D. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

II. Continued Therapy

A. Paroxysmal Nocturnal Hemoglobinuria and Atypical Hemolytic Uremic Syndrome (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy (*see Appendix D*);
3. If request is for a dose increase, new dose does not exceed (a or b):
   a. For PNH: 900 mg every 2 weeks;
   b. For aHUS: 1,200 mg every 2 weeks.

Approval duration: 6 months

B. Generalized Myasthenia Gravis (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;

2. Member is responding positively to therapy as evidenced by a 2-point reduction in MG-ADL total score;
3. If request is for a dose increase, new dose does not exceed 1,200 mg every 2 weeks.

Approval duration: 6 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit or evidence of coverage documents;

B. STEC-HUS.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AchR: acetylcholine receptor
aHUS: atypical hemolytic uremic syndrome
FDA: Food and Drug Administration
gMG: generalized myasthenia gravis
LDH: lactate dehydrogenase
MG-ADL: Myasthenia Gravis-Activities of Daily Living
MGFA: Myasthenia Gravis Foundation of America Clinical Classification
PNH: paroxysmal nocturnal hemoglobinuria
STEC-HUS: Shiga toxin E. coli related hemolytic uremic syndrom

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Corticosteroids		
betamethasone	Oral: 0.6 to 7.2 mg PO per day	7.2mg/day
dexamethasone	Oral: 0.75 to 9 mg/day PO	9 mg/day
methylprednisolone	Oral: 12 to 20 mg PO per day; increase as needed by 4 mg every 2-3 days until there is marked clinical improvement or to a maximum of 40 mg/day	40 mg/day
prednisone	Oral: 15 mg/day to 20 mg/day; increase by 5 mg every 2-3 days as needed. Maximum: 60 mg/day	60 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Cholinesterase Inhibitors		
pyridostigmine (Mestinon®, Regonol®)	Oral immediate release: 600 mg daily in divided doses (range, 60-1500 mg daily in divided doses) Oral sustained release: 180-540 mg QD or BID IV or IM: 2 mg every 2-3 hours	See regimen
neostigmine (Bloxiverz®)	Oral: 15 mg TID. The daily dosage should be gradually increased at intervals of 1 or more days. The usual maintenance dosage is 15-375 mg/day (average 150 mg) IM or SC: 0.5 mg based on response to therapy	See regimen
Immunosuppressants		
azathioprine (Imuran®)	Oral: 50 mg QD for 1 week, then increase gradually to 2 to 3 mg/kg/day	3 mg/kg/day
mycophenolate mofetil (Cellcept®)*	Oral: Dosage not established. 1 gram BID has been used with adjunctive corticosteroids or other non-steroidal immunosuppressive medications	2 g/day
cyclosporine (Sandimmune®)*	Oral: initial dose of cyclosporine (Non-modified), 5 mg/kg/day in 2 divided doses	5 mg/kg/day
Rituxan® (rituximab)*†	IV: 375 mg/m^2 once a week for 4 weeks; an additional 375 mg/m^2 dose may be given every 1 to 3 months afterwards	375 mg/m^2

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*
†*Prior authorization is required for Rituxan*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): unresolved serious Neisseria meningitidis infection, patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection
- Boxed warning(s): serious meningococcal infections

Appendix D: General Information

- Soliris is only available through a REMS (Risk Evaluation and Mitigation Strategy) program due to the risk of life-threatening and fatal meningococcal infection. Patients should be vaccinated with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of Soliris and revaccinated according to current medical guidelines for vaccine use. Patients should be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics if necessary.
- The Advisory Committee on Immunization Practices (ACIP)'s recommendations regarding the meningococcal vaccine are found here: http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html
- Examples of positive response to therapy include:

- PNH: improved measures of intravascular hemolysis (e.g., normalization of lactate dehydrogenase [LDH]), reduced need for red blood cell transfusions, less fatigue, improved health-related quality of life, fewer thrombotic events;
- aHUS: decreased need for plasma therapy (plasma exchange or plasma infusion), decreased need for dialysis, increased glomerular filtration rate, normalization of platelet counts and/or LDH levels;
- gMG: A 2-point reduction in MG-ADL total score is considered a clinically meaningful improvement. The scale can be accessed here: http://www.myasthenia.org/HealthProfessionals/EducationalMaterials.aspx

- The MGFA classification has some subjectivity in it when it comes to distinguishing mild (Class II) from moderate (Class III) and moderate (Class III) from severe (Class IV). Furthermore, it is insensitive to change from one visit to the next.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
PNH	IV infusion: 600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter	900 mg/dose
aHUS	IV infusion: 900 mg weekly for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter	1,200 mg/dose
gMG	IV infusion: 900 mg every 7 days for the first 4 weeks, followed by a single dose of 1,200 mg 7 days after the fourth dose, and then 1,200 mg every 2 weeks thereafter	1,200 mg/dose

VI. Product Availability

Single-dose vials: 300 mg/30 mL

VII. References

1. Soliris Prescribing Information. New Haven, CT: Alexion Pharmaceuticals, Inc.; July 2018. Available at www.soliris.com. Accessed October 12, 2018.
2. Borowitz MJ, Craig FE, DiGiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry Part B (Clinical Cytometry). 2010; 78B: 211–230.
3. CDC. Meningococcal ACIP Vaccine Recommendations. Advisory Committee for Immunization Practices (ACIP). MMWR 2015. Available at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html. Accessed October 16, 2018.
4. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2016; 31: 15-39.
5. Howard JF, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicenter study. Lancet Neurol. 2017; 16(12): 976-986.

6. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidelines for the management of myasthenia gravis. Neurology. 2016; 87: 419-425.
7. Muppidi S. The myasthenia gravis-specific activities of daily living profile. Ann N Y Acad Sci. 2012; 1274:114-119.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1300	Injection, eculizumab 10 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy converted to new template. Age, dosing, and monitoring criteria added per PI; diagnostic criteria edited as follows: PNH: "type III red" is removed – does not have to be RBCs; thrombosis edited to be any thrombosis and not limited by PNH clonal size; specific LDH and Hgb levels deleted; App C - "disabling symptom ms" – is incorporated directly into the diagnostic criteria set. aHUS: the required clinical triad is edited to read AND rather than AND/OR. Efficacy criteria on re-auth splits information from App E, which is a combo of efficacy criteria for the two disease states, and places it directly into the appropriate disease state criteria set.	03.16	04.16
Removed requirement of *Streptococcus pneumoniae* and *Haemophilus influenza type b* (Hib) infections. Modified initial and approval duration to 6 months and 12 months respectively. Removed age requirements. Added max dose to continued approval criteria	03.17	04.17
1Q18 Annual Review Policies combined for Centene Medicaid and Commercial lines of business. Medicaid: For PNH, removed conditions constituting severe PNH that are not objective/specific. Modified requirement for 4 transfusions in last 12 months to 1 transfusion in the last 24 months per the inclusion criteria of the second pivotal trial for approval. For aHUS, removed requirements for specific clinical presentation as a specialist is required to be involved in the care. Removed requirement for causes of aHUS to be ruled out as this is non-specific and under the purview of the provider. For PNH and aHUS,	11.13.17	02.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
removed contraindication for Neisseria meningitidis infection as this is covered by the REMS program. Commercial: For PNH, added prescriber requirement. Removed requirement for baseline platelet count ≥ 30,000/microliter (a clinical trial inclusion criterion). Modified requirement for "history of major adverse vascular events from thromboembolism" to "history of thrombosis". For aHUS, added prescriber requirement. Both: Added age requirements per prescribing information. Added nephrologist as a prescriber option for aHUS. Removed criteria surrounding meningococcal vaccination as this is covered by the Soliris REMS program. Added STEC-HUS as an indication not covered. Modified all approval durations to 6 months.		
Added generalized myasthenia gravis indication and criteria for approval.	12.12.17	02.18
Added note to appendix B that prior authorization is required for Rituxan.	09.13.18	
1Q 2019 annual review: added HIM-Medical Benefit; no significant changes; references reviewed and updated.	10.12.18	02.19

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a

discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.