Clinical Policy: Eculizumab (Soliris)
Reference Number: CP.PHAR.97
Effective Date: 03.01.12
Last Review Date: 11.19
Line of Business: Commercial, Medicaid, HIM-Medical Benefit

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
- Adult patients with neuromyelitis optica spectrum disorder who are anti-aquaporin-4 (AQP4) 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 detectable GPI-deficient hematopoietic clones or ≥ 10% PNH cells;
   5. Member meets one of the following (a or b):
      a. History of ≥ 1 red blood cell transfusion in the past 24 months and (i or ii):
         i. Documentation of hemoglobin < 7 g/dL in members without anemia symptoms;
         ii. Documentation of hemoglobin < 9 g/dL in members with anemia symptoms;
      b. History of 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 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. Neuromyelitis Optica Spectrum Disorder** (must meet all):
1. Diagnosis of NMOSD;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Member has positive serologic test for anti-AQP4 antibodies;
5. Member has experienced at least one relapse within the previous 12 months;
6. Member meets one of the following (a or b):
   a. History of at least two relapses during the previous 12 months;
   b. History of three relapses during the previous 24 months;
7. Baseline expanded disability status score (EDSS) score of ≤ 7;
8. 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**
E. 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 as evidenced by, including but not limited to, improvement in any of the following parameters:
      a. Improved measures of intravascular hemolysis (e.g., normalization of lactate dehydrogenase [LDH]);
      b. Reduced need for red blood cell transfusions;
      c. Increased or stabilization of hemoglobin levels;
      d. Less fatigue;
      e. Improved health-related quality of life;
      f. Fewer thrombotic events;
   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. Neuromyelitis Optica Spectrum Disorder (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 – including but not limited to improvement or stabilization in any of the following parameters:
      a. Frequency of relapse;
      b. EDSS;
      c. Visual acuity;
   3. If request is for a dose increase, new dose does not exceed 1,200 mg every 2 weeks.
   
   Approval duration: 6 months
D. 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
   - AQP-4: Aquaporin-4
   - EDSS: Decrease in Expanded Disability Status Scale
   - 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 syndrome

   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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
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<tr>
<td>betamethasone</td>
<td>Oral: 0.6 to 7.2 mg PO per day</td>
<td>7.2 mg/day</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>Oral: 0.75 to 9 mg/day PO</td>
<td>9 mg/day</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>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</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>prednisone</td>
<td>Oral: 15 mg/day to 20 mg/day; increase by 5 mg every 2-3 days as needed. Maximum: 60 mg/day</td>
<td>60 mg/day</td>
</tr>
<tr>
<td><strong>Cholinesterase Inhibitors</strong></td>
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<td></td>
</tr>
<tr>
<td>pyridostigmine (Mestinon®, Regonol®)</td>
<td>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</td>
<td>See regimen</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/Maximum Dose</td>
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<tr>
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<tr>
<td><strong>neostigmine</strong> (Bloxiverz®)</td>
<td>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</td>
<td>See regimen</td>
</tr>
<tr>
<td><strong>azathioprine</strong> (Imuran®)</td>
<td>Oral: 50 mg QD for 1 week, then increase gradually to 2 to 3 mg/kg/day</td>
<td>3 mg/kg/day</td>
</tr>
<tr>
<td><strong>mycophenolate mofetil</strong> (Cellcept®)*</td>
<td>Oral: Dosage not established. 1 gram BID has been used with adjunctive corticosteroids or other non-steroidal immunosuppressive medications</td>
<td>2 g/day</td>
</tr>
<tr>
<td><strong>cyclosporine</strong> (Sandimmune®)*</td>
<td>Oral: initial dose of cyclosporine (Non-modified), 5 mg/kg/day in 2 divided doses</td>
<td>5 mg/kg/day</td>
</tr>
<tr>
<td><strong>Rituxan®</strong> (rituximab)*†</td>
<td>IV: 375 mg/m² once a week for 4 weeks; an additional 375 mg/m² dose may be given every 1 to 3 months afterwards</td>
<td>375 mg/m²</td>
</tr>
</tbody>
</table>

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;
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- 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
- NMOSD: Stabilization or reduction in EDSS total score. EDSS ranges from 0 (no disability) to 10 (death).

- 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.
- Aquaporin-4 (AQP-4): AQP-4-IgG-seropositive status is confirmed with the use of commercially available cell-binding kit assay (Euroimmun).

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNH</td>
<td>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</td>
<td>900 mg/dose</td>
</tr>
<tr>
<td>aHUS</td>
<td>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</td>
<td>1,200 mg/dose</td>
</tr>
<tr>
<td>gMG, NMOSD</td>
<td>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</td>
<td>1,200 mg/dose</td>
</tr>
</tbody>
</table>

VI. Product Availability
Single-dose vials: 300 mg/30 mL

VII. References

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.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1300</td>
<td>Injection, eculizumab 10 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reviews, Revisions, and Approvals

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.
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

Policy converted 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, 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.
- Added note to appendix B that prior authorization is required for Rituxan.
- 1Q 2019 annual review: added HIM-Medical Benefit; no significant changes; references reviewed and updated.
- Aligned criteria with Ultomiris policy; for PNH, allowed documentation of detectable GPI-deficient hematopoietic clones for flow cytometry; specified examples of positive response to therapy in Section II.A; references reviewed and updated.
- Criteria added for new FDA indication: neuromyelitis optica spectrum disorder; references reviewed and updated.

### 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.

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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.

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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.

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