Medical Guideline Disclaimer

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Definition

Soliris is a monoclonal antibody that binds with high affinity to compliment protein C5, which inhibits its cleavage to C5a and C5b and prevents the generation of the terminal complement complex C5b-9. In patients with paroxysmal nocturnal hemoglobinuria (PNH), eculizumab inhibits terminal complement mediated intravascular hemolysis and in patients with acquired hemolytic uremic syndrome, eculizumab inhibits complement-mediated thrombotic microangiopathy. The precise mechanism by which eculizumab exerts its therapeutic effect in neuromyelitis optica spectrum disorder (NMOSD) is unknown, but is presumed to involve inhibition of aquaporin-4-antibody induced terminal complement C5b-9 deposition

Length of Authorization

PNH and aHUS: Coverage will be provided for twelve months and may be renewed.

gMG: Initial coverage will be provided for 6 months and may be renewed annually thereafter.

NMOSD: Initial authorization will be for no more than 6 months and reauthorization will be for no more than 12 months.
Dosing Limits

A. Max Units (per dose and over time) [Medical Benefit]:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Loading Doses</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNH</td>
<td>60 billable units Days 1, 8, 15, &amp; 22; then 90 billable units Day 29</td>
<td>90 billable units every 14 days</td>
</tr>
<tr>
<td>aHUS, gMG</td>
<td>90 billable units Days 1, 8, 15, &amp; 22; then 120 billable units Day 29</td>
<td>120 billable units every 14 days</td>
</tr>
</tbody>
</table>

I. Initial Approval Criteria

- Soliris must be requested by one of the following specialists:
  - PNH – Hematologist; OR
  - Atypical hemolytic uremic syndrome – Hematologist or Nephrologist; AND

- Patient does not have a systemic infection; AND

- Patients must be administered a meningococcal vaccine at least two weeks prior to initiation of Soliris therapy and revaccinated according to current medical guidelines for vaccine use; AND

- Prescriber is enrolled in the Soliris Risk Evaluation and Mitigation Strategy (REMS) program; AND

Coverage is provided in the following conditions:

Paroxysmal Nocturnal Hemoglobinuria (PNH) †

- Patient is 18 years or older; AND

- Diagnosis must be accompanied by detection of PNH clones by flow cytometry diagnostic testing; AND
  - Demonstrate the presence of at least 2 different glycosylphosphatidylinositol (GPI) protein deficiencies (e.g. CD55, CD59, etc.) within at least 2 different cell lines (granulocytes, monocytes, erythrocytes); AND

- Patient has one of the following indications for therapy:
  - Presence of a thrombotic event
  - Presence of organ damage secondary to chronic hemolysis
  - Patient is pregnant and potential benefit outweighs potential fetal risk
  - Patient is transfusion dependent
  - Patient has high LDH activity (defined as ≥1.5 x ULN) with clinical symptoms

- Documented baseline values for one or more of the following (necessary for renewal): serum lactate dehydrogenase (LDH), hemoglobin level, and packed RBC transfusion requirement
Atypical Hemolytic Uremic Syndrome (aHUS) †

- Patient is 2 months or older; AND
- Thrombotic Thrombocytopenic Purpura (TTP) has been ruled out by evaluating ADAMTS-13 level (ADAMTS-13 activity level > 10%); AND
- Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS) has been ruled out; AND
- Other causes have been ruled out such as coexisting diseases or conditions (e.g. bone marrow transplantation, solid organ transplantation, malignancy, autoimmune disorder, drug-induced, malignant hypertension, HIV infection, etc.), Streptococcus pneumoniae or Influenza A (H1N1) infection, or cobalamin deficiency; AND
- Documented baseline values for one or more of the following (necessary for renewal): serum lactate dehydrogenase (LDH), serum creatinine/eGFR, platelet count, and plasma exchange/infusion requirement

Generalized Myasthenia Gravis (gMG) †

- Patient is 18 years or older; AND
- Patient has Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of Class II to IV disease; AND
- Patient has a positive serologic test for anti-acetylcholine receptor (AchR) antibodies; AND
- Physician has assessed the baseline Quantitative Myasthenia Gravis (QMG) score; AND
- Patient has a MG-Activities of Daily Living (MG-ADL) total score of ≥6; AND
- Patient has failed treatment over at least 1 year with at least 2 immunosuppressive therapies (e.g. azathioprine, cyclosporine, mycophenolate, etc.), or has failed at least 1 immunosuppressive therapy and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIG)

Neuromyelitis Optica Spectrum Disorder (NMOSD) †

- Patient is 18 years or older; AND
- Submission of medical records (e.g. chart notes, laboratory values, etc.) to support the diagnosis of neuromyelitis optica spectrum disorder (NMOSD) by a neurologist confirming all of the following.
- Past medical history of one of the following:
  - Optic neuritis
  - Acute myelitis
• Area postrema syndrome; episode of otherwise unexplained hiccups or nausea and vomiting
• Acute brainstem syndrome
• Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
• Symptomatic cerebral syndrome with NMOSD-typical brain lesions; AND
• Positive serologic test for anti-aquaporin-4 immunoglobulin G (AQP4-IgG)/NMP-IgG antibodies; AND
• Diagnosis of multiple sclerosis or other diagnoses have been ruled out; AND
• Patient has not failed a previous course of Soliris therapy; AND
• History of failure of, contraindication, or intolerance to rituximab therapy; AND
• One of the following:
  • History of at least two relapses during the previous 12 months prior to initiating Soliris
  • History of at least three relapses during the previous 24 months, at least one relapse occurring within the past 12 months prior to initiating Soliris; AND
• Soliris is initiated and titrated according to the US FDA labeled dosing for NMOSD, up to a maximum of 1200mg every 2 weeks; AND
• Prescribed by a neurologist; AND
• Patient is not receiving Soliris in combination with any of the following:
  a. Disease modifying therapies for the treatment of multiple sclerosis (e.g. Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.)
  b. Anti-IL6 therapy (e.g., Actemra (tocilizumab); AND

† FDA Approved Indication(s)

II. Renewal Criteria

Coverage may be renewed based upon the following criteria:
• Patient continues to meet the criteria identified in section III; AND
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: serious meningococcal infections (septicemia and/or meningitis), infusion reactions, serious infections, thrombotic microangiopathy complications (TMA), etc.; **AND**

- Disease response indicated by one or more of the following:
  - **PNH**
    - Decrease in serum LDH from pretreatment baseline
    - Stabilization/improvement in hemoglobin level from pretreatment baseline
    - Decrease in packed RBC transfusion requirement from pretreatment baseline
  - **aHUS**
    - Decrease in serum LDH from pretreatment baseline
    - Stabilization/improvement in serum creatinine/eGFR from pretreatment baseline
    - Increase in platelet count from pretreatment baseline
    - Decrease in plasma exchange/infusion requirement from pretreatment baseline
  - **gMG**
    - Improvement of at least 3-points from baseline in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) total score
    - Improvement of at least 5-points from baseline in the Quantitative Myasthenia Gravis (QMG) total score
  - **NMOSD**
    - Reduction in the number and/or severity of relapses or signs and symptoms of NMOSD
    - Maintenance, reduction, or discontinuation of dose(s) of any baseline immunosuppressive therapy (IST) prior to starting Soliris. **Note:** Add on, dose escalation of IST, or additional rescue therapy will be considered as treatment and failure. **AND**
    - Soliris is dosed according to the FDA labeled dosing for NMOSD: up to a maximum of 1200mg every 2 weeks; **and**
    - Prescribed by a neurologist; **and**
    - Patient is **not** receiving Soliris in combination with **any** of the following:
      a. Disease modifying therapies for the treatment of multiple sclerosis (e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.)
      b. Anti-IL6 therapy [e.g., Actemra (tocilizumab)] **AND**
    - Reauthorization will be for no more than 12 months
III. Dosage/Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paroxysmal nocturnal hemoglobinuria (PNH)</strong></td>
<td>Loading dose: ◦ 600 mg intravenously every 7 days for the first 4 weeks, followed by 900 mg intravenously for the fifth dose 7 days later</td>
</tr>
<tr>
<td>Maintenance dose: ◦ 900 mg intravenously every 14 days</td>
<td></td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>Loading dose: ◦ 900 mg intravenously every 7 days for the first 4 weeks, followed by 1,200 mg intravenously for the fifth dose 7 days later</td>
</tr>
<tr>
<td>Maintenance dose: ◦ 1200 mg intravenously every 14 days</td>
<td></td>
</tr>
<tr>
<td><strong>Atypical hemolytic uremic syndrome (aHUS)</strong></td>
<td>Loading dose: ◦ 300 mg weekly x 1 dose, 300 mg at week 2, then 300 mg every 3 weeks</td>
</tr>
<tr>
<td><strong>Patients &lt; 18 years</strong></td>
<td>Loading dose: ◦ 600 mg weekly x 1 dose, 300 mg at week 2, then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5 kg - &lt;10 kg:</td>
<td>Loading dose: ◦ 600 mg weekly x 2 doses, 600 mg at week 3, then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10 kg - &lt;20 kg:</td>
<td>Loading dose: ◦ 600 mg weekly x 2 doses, 900 mg at week 3, then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>20 kg - &lt;30 kg:</td>
<td>Loading dose: ◦ 900 mg weekly x 4 doses, 1200 mg at week 5, then 1200 mg every 2 weeks</td>
</tr>
<tr>
<td><strong>Generalized Myasthenia Gravis (gMG)</strong></td>
<td>Loading dose: ◦ 900 mg intravenously every 7 days for the first 4 weeks, followed by 1,200 mg intravenously for the fifth dose 7 days later</td>
</tr>
<tr>
<td>Maintenance dose: ◦ 1200 mg intravenously every 14 days</td>
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</tbody>
</table>

**Dose Adjustment for aHUS (adult and pediatric patients) and gMG (adult patients) in case of Plasmapheresis, Plasma Exchange or Fresh Frozen Plasma Infusion**

<table>
<thead>
<tr>
<th>Type of Plasma Intervention</th>
<th>Most Recent Soliris Dose</th>
<th>Supplemental Soliris With Each Plasma Intervention</th>
<th>Timing of Supplemental Soliris Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis or plasma exchange (PE)</td>
<td>300 mg</td>
<td>300 mg per each plasmapheresis or PE</td>
<td>Within 60 minutes after each plasmapheresis or PE</td>
</tr>
<tr>
<td>≥ 600 mg</td>
<td>600 mg per each plasmapheresis or PE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Fresh frozen plasma infusion (FFP)

<table>
<thead>
<tr>
<th>Infusion</th>
<th>≥ 300 mg</th>
<th>300 mg per each infusion of FFP</th>
<th>60 minutes prior to each infusion of FFP</th>
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*Doses should be administered at the above intervals, or within two days of these time points.*

### Limitations/Exclusions

Soliris® (eculizumab) is not considered medically necessary for indications other than those listed above due to insufficient evidence of therapeutic value.

### Applicable Procedure Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1300</td>
<td>Injection, eculizumab, 10 mg</td>
</tr>
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</table>

### Applicable NDCs

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>25682-0001-xx</td>
<td>Soliris 300 mg/30 mL single-use vials for injection</td>
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</table>

### Applicable Diagnosis Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>D59.3</td>
<td>Hemolytic-uremic syndrome</td>
</tr>
<tr>
<td>D59.5</td>
<td>Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]</td>
</tr>
<tr>
<td>G36.0</td>
<td>Neuromyelitis Optica Spectrum Disorder (NMOSD)</td>
</tr>
<tr>
<td>G70.00</td>
<td>Myasthenia gravis without (acute) exacerbation</td>
</tr>
<tr>
<td>G70.01</td>
<td>Myasthenia gravis with (acute) exacerbation</td>
</tr>
</tbody>
</table>

### Revision History

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>10/02/2019</td>
<td>Added the new indication for Neuromyelitis Optica Spectrum Disorder (NMOSD), added the criteria and it’s diagnosis code G36.0</td>
</tr>
</tbody>
</table>

### IV. References

3. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. Hillmen P; Hall C; Marsh JC; Elebute M; Bombara MP; Petro BE; Cullen MJ; Richards SJ; Rollins SA; Mojcik CF; Rother RP. N Engl J Med 2004 Feb 5;350(6):552-9.

4. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. Hillmen P; Young NS; Schubert J; Brodsky RA; Socie G; Muus P; Roth A; Szer J; Elebute MO; Nakamura R; Browne P; Risitano AM; Hill A; Schrezenmeier H; Fu CL; Maciejewski J; Rollins SA; Mojcik CF; Rother RP; Luzzatto L. N Engl J Med. 2006 Sep 21;355(12):1233-43.

5. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Brodsky RA; Young NS; Antonioli E; Risitano AM; Schrezenmeier H; Schubert J; Gaya A; Coyle L; de Castro C; Fu CL; Maciejewski JP; Bessler M; Kroon HA; Rother RP; Hillmen P. Blood. 2008 Feb 15;111(4):1840-7. Epub 2007 Nov 30.


