Policy Title:	Soliris (eculizumab) and Ultomiris (ravulizumab) (**NON HEMATOLOGY POLICY** Intravenous		
		Department:	PHA
Effective Date:	01/01/2020		
Review Date:	09/18/2019, 12/20/2019, 1/22/2020, 12/2020, 5/27/2021, 3/3/2022, 8/4/2022, 4/27/2023, 12/14/2023, 01/10/2024, 05/08/2024		

Purpose: To support safe, effective, and appropriate use of Soliris (eculizumab) and Ultomiris (ravulizumab).

Scope: Medicaid, Commercial, Medicare-Medicaid Plan (MMP)

Policy Statement:

Soliris (eculizumab) and Ultomiris (ravulizumab) are covered under the Medical Benefit when used within the following guidelines. Use outside of these guidelines may result in non-payment unless approved under an exception process. **For Hematology indications, please refer to the NHPRI Soliris or Ultomiris Hematology Policy.**

Summary of Evidence:
Clinical trials evaluating the efficacy and safety of C5 complement inhibitors have demonstrated their effectiveness in reducing hemolysis, transfusion requirements, and the risk of thromboembolic events in patients with PNH. Studies have shown that treatment with eculizumab or ravulizumab leads to a significant reduction in intravascular hemolysis, as evidenced by decreased lactate dehydrogenase (LDH) levels and reduced need for red blood cell transfusions. C5 complement inhibitors have been shown to improve quality of life and overall survival in patients with PNH.

Procedure:

Coverage of Soliris (eculizumab) and Ultomiris (ravulizumab) will be reviewed prospectively via the prior authorization process based on criteria below.

Initial Criteria:

- MMP members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements.
- Patient is at least 18 years of age (unless otherwise specified); AND
- Patient must be vaccinated against meningococcal disease at least two weeks prior to initiation of therapy and will continue to be revaccinated according to current medical guidelines for vaccine use; AND
- Patient does not have an unresolved, serious systemic infection (e.g., *Neisseria meningitidis*, etc.); AND

- Will not be used in combination with other immunomodulatory biologic therapies (e.g., Rituxan (rituximab), Soliris (eculizumab), Ultomiris (ravulizumab), Empaveli or Syfovre (pegcetacoplan), Enspryng (satralizumab), Uplizna(inebilizumab), Vyvgart/Vyvgart Hytrulo (efgartigimod), Rystiggo(rozanolixizumab), Veopoz (pozelimab), etc.); AND

Neuromyelitis optica spectrum disorder (NMOSD) for Soliris and Ultomiris

- 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)/NMO-IgG antibodies; AND
    - Alternative diagnoses have been excluded [e.g., myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOGAD), multiple sclerosis, sarcoidosis, cancer, chronic infection, etc.]; AND
- Patient has not failed a previous course of Soliris (eculizumab) or Ultorimis (ravulizumab) therapy; AND
- Patient has a history of at least two relapses during the previous 12 months prior to starting therapy OR three relapses during the previous 24 months, with at least one relapse occurring within the past 12 months prior to initiating therapy; AND
- Prescribed by, or in consultation with, a neurologist; AND
- Patient has an Expanded Disability Status Score (EDSS) of ≤ 7.0 (i.e., presence of at least limited ambulation with aid); AND
- Patients who are receiving concurrent corticosteroid therapy are on ≤20 mg per day and those receiving immunosuppressive therapy (e.g. azathioprine, glucocorticoids, mycophenolate, etc.) are on a stable dose regimen; AND
- Patient has not received therapy with rituximab or mitoxantrone in the last 3 months; AND
- Patient has not received intravenous immune globulin (IVIG) in the last 3 weeks; AND
- Patient is not receiving Soliris or Ultomiris in combination with each other or with any of the following:
    - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab)]
    - Uplizna (inebilizumab)
    - Rituximab; AND

- Patients that are requesting Soliris must have experienced a failure, contraindication or intolerance to Enspryng (satralizumab)*, Ultorimis (ravulizumab) AND Uplizna (inebilizumab); OR
- Patients that are requesting Ultorimis (ravulizumab) must have experienced a failure, contraindication or intolerance to Enspryng (satralizumab)*, AND Uplizna (inebilizumab)

* This requirement **ONLY** applies to **Medicaid** Members

Generalized myasthenia gravis (gMG) for Soliris and Ultomiris

- Submission of medical records (e.g., chart notes, laboratory values, etc.) to support the diagnosis of generalized myasthenia gravis (gMG); AND
- Prescribed by, or in consultation with a neurologist; AND
- Patient has positive serologic test for anti-acetylcholine receptor (AChR) antibodies; AND
- Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of class II-IV disease§; AND
- Physician has assessed objective signs of neurological weakness and fatigability on a baseline neurological examination (e.g., including, but not limited to, the Quantitative Myasthenia Gravis (QMG) score, etc.); AND
- Patient has a Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL) total score ≥ 6 at initiation of therapy; AND
- Patient had an inadequate response after a minimum one-year trial of concurrent use with two (2) or more immunosuppressive therapies (e.g., corticosteroids plus an immunosuppressant such as azathioprine, methotrexate, cyclosporine, mycophenylate, etc.) OR patient has required at least one acute or chronic treatment with plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIG) in addition to immunosuppressant therapy; AND
- If the patient is requesting Soliris, the patient must have an inadequate response or contraindication to both ravulizumab (Ultomiris) AND efgartigimod (Vyvgart IV) [medical documentation must be provided]; AND
- If the patient is requesting Ultomiris, the patient must have an inadequate response or contraindication to efgartigimod (Vyvgart IV) [medical documentation must be provided]; AND
- Patient will avoid or use with caution medications known to worsen or exacerbate symptoms of MG (e.g., certain antibiotics, beta-blockers, botulinum toxins, hydroxychloroquine, etc.); AND
- Must not be administered with live-attenuated or live vaccines during treatment; AND
    - Patient does not have an active infection, including clinically important localized infections

§ **Myasthenia Gravis Foundation of America (MGFA) Disease Classifications:**

- Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
- Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
  - IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
  - IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
  - IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
  - IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
  - IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
  - IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Continuation of Therapy Criteria:

- **Neuromyelitis optica spectrum disorder (NMOSD)**
  - Patient continues to meet initial criteria; AND
  - Submission of medical records (e.g., chart notes, laboratory tests) to demonstrate a positive clinical response from baseline as demonstrated by at least both of the following:
    - 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 from baseline to treat NMOSD or exacerbation of symptoms while on Soliris therapy will be considered as treatment failure.
  - Soliris is dosed according to the US FDA labeled dosing for NMOSD: up to a maximum of 1200 mg every 2 weeks; AND
  - Prescribed by, or in consultation with, a neurologist; AND
  - Patient is not receiving Soliris in combination with any of the following:
    - Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]
    - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab)]
    - Uplizna (inebilizumab)
    - Vyvgart (efgartigimod)
    - Rituximab

- **Generalized myasthenia gravis (gMG)**
  - Patient continues to meet initial criteria; and
  - Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: serious meningococcal infections (septicemia and/or meningitis), infusion reactions, serious infections, thrombotic microangiopathy complications (TMA), etc; AND
  - Submission of medical records (e.g., chart notes, laboratory tests) to demonstrate a positive clinical response from baseline as demonstrated by 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.
    - Improvement in muscle strength testing with fatigue maneuvers as evidenced on neurologic examination when compared to baseline

Coverage durations:

- Initial coverage: 6 months
- Continuation of therapy coverage: 6 months

Per §§ 42 CFR 422.101, this clinical medical policy only applies to INTEGRITY in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD).

Policy Rationale:
Soliris and Ultomiris was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Soliris and Ultomiris according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For INTEGRITY (Medicare-Medicaid Plan) members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.

Dosage/Administration:

Soliris:

Indication	Dose	Maximum dose (1 billable unit = 10 mg)
Generalized Myasthenia Gravis (gMG) or Neuromyelitis optica spectrum disorder (NMOSD)	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 Maintenance dose: 1200 mg intravenously every 14 days	Loading dose: 90 billable units Days 1, 8, 15, & 22; then 120 billable units Day 29 Maintenance dose: 120 billable units every 14 days

Ultomiris:

<table>
<tr><th>Indication</th><th>Dose</th><th>Maximum dose (1 billable unit = 10 mg)</th></tr>
<tr><td>Generalized Myasthenia Gravis (gMG) or NMOSD</td><td>Administer the loading dose based on weight. Two weeks later, begin maintenance doses at a once every 8-week interval:

<table><tr><th>Body weight range</th><th>Loading dose</th><th>Maintenance dose</th></tr><tr><td>≥40 kg - <60kg</td><td>2400 mg</td><td>3000mg</td></tr><tr><td>≥60 kg - <100kg</td><td>2700mg</td><td>3300mg</td></tr><tr><td>≥100 kg</td><td>3000mg</td><td>3600mg</td></tr></table></td><td>Loading doses:
300 units on day 0
Maintenance Dose:
360 units on day 14 and every 8 weeks thereafter</td></tr>
</table>

Investigational use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

Applicable Codes:
Below is a list of billing codes applicable for covered treatment options. The below tables are provided for reference purposes and may not be all-inclusive. Requests received with codes from tables below do not guarantee coverage. Requests must meet all criteria provided in the procedure section.

The following HCPCS/CPT code is:

HCPCS/CPT Code	Description
J1300	Injection, eculizumab, 10 mg
J1303	Injection, ravulizumab-cwvz, 10mg

References:

1. Soliris [package insert]. New Haven, CT: Alexion Pharmaceuticals, Inc.; July 2022.
2. Ultomiris [package insert]. New Haven, CT: Alexion Pharmaceuticals, Inc.; April 2023.
3. Sanders D, Wolfe G, Benatar M et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016; 87 (4):419-425.
4. Jaretzki A, Barohn RJ, Ernstoff RM et al. Myasthenia Gravis: Recommendations for Clinical Research Standards. *Ann Thorac Surg*. 2000;70: 327-34.
5. Howard JF, Utsugisawa K, Benatar M. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN); a phase 3, randomized, double-blind, placebo-controlled, multicenter study. *Lancet Neurol*. 2017 Oct 20. http://dx.doi.org/10.1016/S1474-4422(17)30369-1Ingenix HCPCS Level II, Expert 2011