DRUG DETERMINATION POLICY

Title: DDP-03 Soliris and Ultomiris

Effective Date: 12/15/2020

Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

1.0 Policy:

This policy describes the determination process for coverage of specific drugs that require prior approval.

This policy does not guarantee or approve Benefits. Coverage depends on the specific Benefit plan. Pharmacy Benefit Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

2.0 Background or Purpose:

Soliris (eculizumab) and Ultomiris (ravulizumab) are specialty drugs indicated for different diagnoses and are associated with significant toxicity. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and mitigation of toxicity, if possible.

3.0 Clinical Determination Guidelines:

Document the following with chart notes:

A. General Considerations.

   1. Coverage of Soliris and Ultomiris is subject to provisions as described in DDP-08 "Site of Care for Administration of Parenteral Specialty Medications."

   2. Exclusions: coverage for non-FDA approved indications.

B. Paroxysmal Nocturnal Hemoglobinuria (PNH) [must meet all listed below]:

   1. Age: at least 18 years.

   2. Prescriber: hematologist or nephrologist.

   3. Diagnosis and severity [must meet all listed below]:

a. Flow cytometry: greater than two different Glycosylphosphatidylinositol (GPI) protein deficiencies within two different cell lines from granulocytes, monocytes, or erythrocytes.

b. Transfusion dependent [must meet one listed below]:

- Hemoglobin (Hgb): at or below 7 g/dL.
- Hemoglobin (Hgb): at or below 9 g/dL and experiencing symptoms of anemia.

c. Lactate dehydrogenase (LDH) level: 1.5 times the upper limit of normal range.

4. Dosage Regimen (see Appendix I):

5. Approval.

a. Initial: six months.

b. Re-approval: six months (must meet both below):

- LDH level shows reduction from baseline within three months' time.
- Hemoglobin (Hgb) stabilized: did not require a transfusion and Hgb 7 to 9g/dL (depending on baseline).

C. Atypical Hemolytic Uremic Syndrome (aHUS)

1. Age: at least two months.

2. Prescriber: hematologist or nephrologist.

3. Diagnosis and severity [must meet both listed below]:

a. Signs and symptoms: microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury.

b. Rule out: Shiga Toxin *E. coli*-related Hemolytic Uremic Syndrome (STEC-HUS).

4. Dosage regimen: see Appendix I.

5. Approval:

a. Initial: six months.

b. Re-approval: six months [must meet one listed below]:

- Increase in platelet count from baseline.
- Maintenance of normal platelet count and LDH levels for at least four weeks.
- 25 percent reduction in serum creatinine for at least four weeks.
- Lack of decrease platelets greater than 25 percent from baseline for at least two weeks, plasma exchange or infusion and new dialysis requirement.

D. Generalized Myasthenia Gravis (MG).

1. Prescriber: neurologist.

2. Diagnosis and severity.

    a. Anti-acetylcholine receptor (AChR) antibodies: positive serologic test.

    b. Severity [must meet both listed below] (see Appendix II/III):

        - Glial Fibrillary Acidic (GFA) Clinical Classification of class: II, III, or IV.

        - Myasthenia Gravis Activities of Daily Living (MG-ADL): total score at least 6 at initiation of therapy.

3. Other therapies: contraindicated, inadequate response or had significant adverse effects [must meet both listed below]:

    a. Immunosuppressive therapy [must try two DMARD's listed below]:

        - Conventional traditional disease-modifying anti-rheumatic drugs (DMARDs): azathioprine, methotrexate, cyclosporine, or mycophenolate for four to six weeks each over a one year time-period.

    b. Alternative treatment [must try one therapy listed below]:

        - Intravenous immune globulin (IVIG) over one year.

        - Plasmapheresis or plasma exchange two times over a one year period.

4. Dosage regimen: see Appendix I.

5. Approval:

    a. Initial: one month in combination with a stable regimen of immunosuppressive treatment.

    b. Re-approval: two months with usual total treat duration of 12 weeks [must meet both listed below]:

        - Baseline immunosuppressive therapy (prior to starting Soliris or Ultomiris): maintenance, decrease, or discontinue.

        - Myasthenia Gravis-activities of daily living: three-point improvement and/or maintenance of score from baseline.

    c. Treatment failure: no improvement in four weeks as shown by add-on treatment, increased dose of immunosuppressive treatment, or additional Myasthenia Gravis rescue therapy from baseline.

F. Neuromyelitis optica spectrum disorder.

1. Age: 18 years.

2. Prescriber: neurologist.

3. Diagnosis and severity [must meet all listed below]:

a. Antibody: anti-aquaporin-4 (AQP4) antibody positive.

b. At least one core clinical characteristics: Optic neuritis; Acute myelitis; Area postrema syndrome; Acute brainstem syndrome; Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions; Symptomatic cerebral syndrome with NMOSD-typical brain lesions.

c. Relapses: at least two relapses in the last year or three relapses in the last two years with at least one relapse one year prior.

d. Expanded Disability Status Scale (EDSS) score at or below seven (consistent with the presence of at least limited ambulation with aid)

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4. Other therapies: contraindication, inadequate response or significant side effects to all therapies listed below:

   a. Acute attacks: high dose methylprednisolone (one gram for three to five days) and if unresponsive plasma exchange every other day for up to seven exchanges.

   b. Immunosuppressive agents azathioprine, mycophenolate, methotrexate.

   c. Biologicals: Actemra, Rituxan, Enspryng.

5. Dosage regimen (see Appendix I):

6. Approval.

   a. Initial: six months in combination with a stable regimen of immunosuppressive treatment.

   b. Reapproval: six months; reduced symptoms.

4.0 Coding:

CODES AFFECTED				
Code	**Brand**	**Generic**	**Billing (1u)**	**Prior Approval Required**
J1300	Soliris IV	Eculizumab	10mg	Y
J1303	Ultomiris IV	Ravulizumab-cwvz	NA	Y

5.0 Unique Configuration/Prior Approval/Coverage Details:

None.

6.0 References, Citations & Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Soliris, Ultomiris accessed October 2020.
2. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAN): a phase 3, randomized, double-blind, placebo-controlled, multicenter study. Lancet Neurol 2017;16: 976-86.
3. Myasthenia gravis: new developments in research and treatment. Curr Opin Neurol 2017, 30:464-470.
4. Can eculizumab be discontinued in aHUS? Medicine 2016; 95:31.

5. UpToDate Wolters Kluwer https://www.uptodate.com/contents/neuromyelitis-optica-spectrum-disorders?search=neuromyelitis%20optica%20spectrum%20dis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 accessed October 2020.

7.0 Appendices:

See pages 6-9.

8.0 Revision History:

Original Effective Date: 04/25/2018

Next Review Date: 11/10/2021

Revision Date	Reason for Revision
2/19	Transitioned to new format
12/19	Annual review; replaced abbreviations
10/20	Annual review; added diagnosis Neuromyelitis optica spectrum disorder; added pediatric dosing for adult and Pediatric aHUS; replaced abbreviations, clarified criteria instructions, formatting, approved by P&T Committee 12/9/20
9/21	Code for Ultomiris changed

Appendix I: Dosage Regimens per Diagnosis

Agent	Loading Dose	Maintenance Dose
Soliris IV (eculizumab)		
PNH	600mg weekly x 4	900mg week 5, then 900mg every 2 weeks
aHUS	900mg weekly x 4	1,200mg week 5, then 1,200mg every 2 weeks. PPH: Last dose ≥ 600mg give 600mg; 300mg give 300mg give 1 hour post
Pediatric aHUS		
5 to <10Kg	300mg weekly x1	300mg @ week 2, then 300mg q 3 weeks.
10 to <20Kg	600mg weekly x1	300mg @ week 2, then 300mg q 2 weeks.
20 to <30Kg	600mg weekly x 2	600mg @ week 3, then 600mg q 2 weeks.
30 to ≤40Kg	600mg weekly x 2	900mg @ week 3, then 900mg q 2 weeks.
≥40Kg	900mg weekly x 4	1200mg @ week 5, then 1200mg q 2 weeks
MG and NOSD	900mg weekly x 4	1,200mg week 5, then 1,200mg every 2 weeks. PPH: Last dose ≥ 600mg give 600mg; 300mg give 300mg give 1 hour post
Ultomiris IV (ravulizunab-cwvz)		
PNH		Two weeks after loading dose:
≥40 to <60Kg	2,400mg	3,000 mg every 8 weeks,
≥60 to <100 kg	2,700mg	3,300 mg every 8 weeks,
≥100 kg	3,000mg	3,600 mg every 8 weeks,
aHUS		Two weeks after loading dose:
≥20 to <30 Kg	900mg	2,100mg every 8 weeks
≥30 to < 40Kg	1,200mg	2,700mg every 8 weeks
≥40 to <60Kg	2,400mg	3,000mg every 8 weeks
≥60 to <100Kg	2,700mg	3,300mg every 8 weeks
≥100Kg	3,000mg	3,600mg every 8 weeks
Pediatric aHUS		Two weeks after loading dose:
5 to <10Kg	600mg	300mg every 4 weeks.
10 to <20Kg	600mg	600mg every 4 weeks.
20 to <30Kg	900mg	1,200mg every 8 weeks
30 to <40Kg	1,200mg	2,700mg every 8 weeks
40 to <60Kg	2,400mg	3,000mg every 8 weeks
60 to <100Kg	2,700mg	3,300mg every 8 weeks
≥100Kg	3,00mg	3,600mg every 8 weeks

PNH - Paroxysmal Nocturnal Hemoglobinuria; PPH - plasmapheresis or plasma exchange.
aHUS - Atypical Hemolytic Uremic Syndrome; MG - Generalized Myasthenia Gravis
NOSD - Neuromyelitis Optica Spectrum Disorder

Appendix II: MGFA Clinical Classification & MG-ADL

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.

A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

B. 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.

A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

B. 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.

A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser Involvement of oropharyngeal muscles.

C. 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.

Appendix III

MG Activities of Daily Living (MG-ADL)

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Total score _____

Appendix IV: Patient Safety and Monitoring

Drug	Adverse Reactions	Monitoring	REMS
Soliris IV Eculizumab IV	• Cardiovascular: tachycardia (20-40%), Peripheral edema (8-29%), hypotension (12-20%) • Central nervous system: headache (17-50%), insomnia (10-24%), fatigue (7-20%) • Dermatological: rash (12-20%), pruritus (6-15%) • Endocrine/metabolism: hypokalemia (10-18%) • Gastrointestinal: diarrhea (20-47%), vomiting (10-47%), nausea (12-40%), ad. pain (8-33%), gastroenteritis (5-20%) • Genitourinary: urinary tract infection (15-35%), uropathy (17%), proteinuria (12-24% • Hematology/oncology: anemia (17-35%), neoplasm (6-30%), leukopenia (12-24%) • Musculoskeletal: weakness (15-20%), back pain (5-19%), arthralgia (6-17%), musculoskeletal pain, muscle spasm • Ophthalmology: eye disease (10-29%) • Renal: renal insufficiency (15-29%) • Respiratory: cough (20-60%), nasopharyngitis (6-17%) nasal congestion (20-40%), upper respiratory infection (URI) (5-40%), rhinitis (22%), bronchitis (10-18%) • Miscellaneous: infection (24%), catheter infection (17%), fever (7-80%)	• Labs: CBC with differential., LDH, Sr Creatinine, AST, urinalysis • Signs and symptoms: meningococcal infection, infusion reaction • aHUS (after discontinuation) thrombotic microangiopathy complications (angina, dyspnea, mental status change, seizure or thrombosis), serum creatinine, LDH, platelets • PNH (after discontinuation): signs and symptoms of intravascular hemolysis (anemia, fatigue, pain, dark urine, dyspnea, thrombosis)	Meningococcal infection awareness Prescriber enrollment in Soliris Risk Evaluation & Mitigation Strategy (REMS) program
Ultomiris IV (ravulizunab-cwvz)	• Central nervous system: headache (32%) • Respiratory: upper respiratory infection (29%)	• Signs and symptoms: meningococcal infection, infusion reaction • After discontinuation: monitor for hemolysis and major vascular events	