DRUG DETERMINATION POLICY

Title: DDP-03 Complement Inhibitors

Effective Date: 12/13/24

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), Ultomiris (ravulizumab) and Empaveli (pegcetacoplan) 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:

I. General Considerations.

- A. Appropriate medication use [must meet one listed below]:
  - 1. Food and Drug Administration (FDA) approval status [must meet one listed below]:
    - a. FDA approved: product, indication, and/or dosage regimen.
    - b. Non-FDA approved: compendium support (Lexicomp®) for the use of a drug for a non-FDA-approved indication or dosage regimen.
  - 2. Place in therapy: sequence of therapy supported by national or internationally accepted guidelines and/or studies (e.g., oncologic, infectious conditions).
- B. Site of Care: these agents are subject to provisions as described in DDP-08 Site of Care for Administration of Parenteral Specialty Medications.
- C. Pharmaceutical sample use: The Plan does not recognize samples as a medication trial or for continuation of therapy.

D. Adherence to requested medication required for re-approval [must meet one listed below]:

1. Medications processed on the medical benefit: consistent utilization (at least 80% of days covered) history documented in claims history or chart notes.
2. Medications processed on the pharmacy benefit: consistent (at least 80% of days covered) fill history electronically or verbally from the pharmacy.

II. Paroxysmal Nocturnal Hemoglobinuria [must meet all listed below]:

A. Age: at least 18 years.

B. Prescriber: hematologist or nephrologist.

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

1. Flow cytometry: greater than two different Glycosylphosphatidylinositol (GPI) protein deficiencies within two different cell lines from granulocytes, monocytes, or erythrocytes.
2. Transfusion dependent [must meet one listed below]:
   a. Hemoglobin (Hgb): at or below 7g per dL.
   b. Hemoglobin (Hgb): at or below 9g per dL and experiencing symptoms of anemia.
3. Lactate dehydrogenase level: 1.5 times the upper limit of normal range.

D. Dosage Regimen: see Appendix I

E. Soliris other therapies: A trial of Ultomiris is required unless contraindicated. The trial must result in an inadequate response after 24 consecutive weeks of use or a severe adverse reaction.

F. Approval.

1. Initial: six months.
2. Re-approval: six months [must meet both listed below]:
   a. Reduction in lactate dehydrogenase from baseline within three months.
   b. Stabilization of Hemoglobin (Hgb): no transfusions required and Hgb 7 to 9g per dL (depending on baseline).

III. Atypical Hemolytic Uremic Syndrome [must meet all listed below]:

A. Age: at least two months.

B. Prescriber: hematologist or nephrologist.

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

1. Signs and symptoms: microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.
2. Rule out: Shiga Toxin *E. coli*-related Hemolytic Uremic Syndrome.

D. Dosage regimen (see Appendix I).

E. Soliris Other Therapies: A trial of Ultomiris is required unless contraindicated. The trial must result in an inadequate response after 24 consecutive weeks of use or a severe adverse reaction.

F. Approval:

1. Initial: six months.
2. Re-approval: six months [must meet one listed below]:

a. Increase in platelet count from baseline.

b. Maintenance of normal platelet count and lactate dehydrogenase levels for at least four weeks.

c. 25 percent reduction in serum creatinine for at least four weeks.

d. Lack of decrease platelets greater than 25 percent from baseline for at least two weeks, plasma exchange or infusion and new dialysis requirement.

IV. Generalized Myasthenia Gravis [must meet all listed below]:

A. Prescriber: neurologist, neuroimmunologist

B. Diagnosis and severity.

1. Anti-acetylcholine receptor antibodies: positive serologic test.

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

a. Myasthenia Gravis Foundation of America Clinical Classification of class: II, III, or IV

b. Myasthenia Gravis Activities of Daily Living: total score at least six at initiation of therapy.

C. Other therapies: inadequate response after trial length as listed below unless significant adverse effects or contraindicated [must meet all listed below]:

1. Immunosuppressive therapy with a trial of two DMARDs for four weeks each.

a. Conventional traditional disease-modifying anti-rheumatic drugs (DMARDs): azathioprine, methotrexate, cyclosporine, or mycophenolate

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

a. Intravenous immune globulin one-year duration.

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

3. Soliris only: Ultomiris for 24 weeks

D. Dosage regimen: see Appendix I

E. Approval:

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

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

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

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

3. Treatment failure: no improvement in four weeks as shown by one listed below:

a. Add-on treatment.

b. Increased dose of immunosuppressive treatment.

c. Additional Myasthenia Gravis rescue therapy from baseline.

V. Neuromyelitis optica spectrum disorder.

A. Age: 18 years.

B. Prescriber: neurologist or neuroimmunologist

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

1. Antibody: anti-aquaporin-4 antibody positive.
2. At least one core clinical characteristic [must meet one listed below]
   a. Optic neuritis.
   b. Acute myelitis.
   c. Area postrema syndrome.
   d. Acute brainstem syndrome.
   e. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions.
   f. Symptomatic cerebral syndrome with NMOSD-typical brain lesions.
3. Relapses [must meet one listed below]:
   a. At least one relapse in the last year
4. Expanded Disability Status Scale (EDSS) score at or below seven (consistent with the presence of at least limited ambulation with aid).

D. Other therapies: inadequate response to prednisone, two immunosuppressive agents listed below, one biological listed below, and Ultomiris (if Soliris is being requested) after the specified trial duration unless significant adverse effects or contraindicated:

1. 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.
2. Immunosuppressive agents: azathioprine, mycophenolate, and methotrexate for four months each.
3. Biologicals: Actemra or Rituxan for four months.
4. Ultomiris for 24 weeks.

E. Dosage regimen (see Appendix I).

F. Approval.

1. Initial: six months in combination with a stable regimen of immunosuppressive treatment.
2. Re-approval: six to twelve months; reduced symptoms or relapses.

4.0 Coding:

COVERED CODES – MEDICAL BENEFIT				
Code	**Brand**	**Generic**	**Billing Units (1 unit)**	**Prior Approval Required**
J1300	Soliris IV	Eculizumab	10 mg	Y
J1303	Ultomiris IV	Ravulizumab-cwvz	10 mg	Y

COVERED PRODUCTS – PHARMACY BENEFIT		
Brand	**Generic**	**Prior Approval Required**
Empaveli SQ	pegcetacoplan SQ	Y

5.0 References, Citations & Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Soliris, Ultomiris, Empaveli accessed October 2021.
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.
6. International Consensus Guidance for Management for Myasthenia Gravis. Neurology 2021;96(3) https://n.neurology.org/content/96/3/114
7. Consensus regarding diagnosis and management of atypical hemolytic uremic syndrome The Korean Journal of Internal Medicine 2020;35(1):25-40
8. Consensus statement for diagnosis and treatment of Paroxysmal Nocturnal Hemoglobinuria. Hematol Transfus Cell Ther. 2021'43(3):341-348.
10. EFNS guidelines on diagnosis and management of neuromyelitisoptica European Journal of Neurology 22010;17:1019-1032

6.0 Appendices:

See pages 7-11.

7.0 Revision History:

Original Effective Date: 04/25/2018

Next Review Date: 11/10/2024

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
10/21	Annual review; added appropriate use section; added Empaveli; changed title to Complement Inhibitors from Soliris and Ultomiris; decreased number of other therapies needed for Neuromyelitis optica; formatting.
10/22	Annual review; added Ultromiris for treatment of MG; clarified instruction in V.C.2; added references
5/23	Off cycle review, clarified other MS therapies, put step therapy for approval of Solirus, added prescriber neuroimmunologist
9/23	Annual Review; updated coding table, added no sample use and adherence component to general considerations section, updated other therapies language

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, MG, and NMOSD	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 10 to <20Kg 20 to <30Kg 30 to ≤40Kg ≥40Kg	 300mg weekly x1 600mg weekly x1 600mg weekly x 2 600mg weekly x 2 900mg weekly x 4	 300mg @ week 2, then 300mg q 3 weeks. 300mg @ week 2, then 300mg q 2 weeks. 600mg @ week 3, then 600mg q 2 weeks. 900mg @ week 3, then 900mg q 2 weeks. 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, MG, and NMOSD ≥40 to <60Kg ≥60 to <100 kg ≥100 kg	 2,400mg 2,700mg 3,000mg	Two weeks after loading dose: 3,000mg every 8 weeks, 3,300mg every 8 weeks, 3,600mg every 8 weeks,
aHUS *≥20 to <30 Kg* *≥30 to < 40Kg* *≥40 to <60Kg* *≥60 to <100Kg* *≥100Kg*	 900mg 1,200mg 2,400mg 2,700mg 3,000mg	Two weeks after loading dose: 2,100mg every 8 weeks 2,700mg every 8 weeks 3,000mg every 8 weeks 3,300mg every 8 weeks 3,600mg every 8 weeks
Pediatric aHUS 5 to <10Kg 10 to <20Kg 20 to <30Kg 30 to <40Kg 40 to <60Kg 60 to <100Kg ≥100Kg	 600mg 600mg 900mg 1,200mg 2,400mg 2,700mg 3,00mg	Two weeks after loading dose: 300mg every 4 weeks. 600mg every 4 weeks. 1,200mg every 8 weeks 2,700mg every 8 weeks 3,000mg every 8 weeks 3,300mg every 8 weeks 3,600mg every 8 weeks
MG, generalized 40 to < 60Kg 60 to < 100mg ≥100kg	 2,400mg 2,700mg 3,000mg	Two weeks after loading dose 3,000mg every 8 weeks 3,300mg every 8 weeks 3,600mg every 2 weeks
Empaveli subcutaneous (pegcetacoplan SQ)		
PNH	1,080mg	Twice weekly

PNH - Paroxysmal Nocturnal Hemoglobinuria; PPH - plasmapheresis or plasma exchange.
aHUS - Atypical Hemolytic Uremic Syndrome; MG - Generalized Myasthenia Gravis
NMOSD - 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	• Cardiovascular: Hypertension (17-59%), tachycardia (20-40%), peripheral edema (8-29%), hypotension (12-20%) • Central Nervous System: headache (17-50%), insomnia (10-24%), fatigue (7-20%), dizziness (15%) • Dermatological: rash (12-22%), pruritus (6-15%) • Endocrine/Metabolism: hypokalemia (10-18%) • Gastrointestinal: diarrhea (16-47%), 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%) • Neuromuscular and skeletal: back pain (5-19%), arthralgia (6-17%), musculoskeletal pain (6-15%), muscle spasm (5-11%) • 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%), influenza (11%), catheter infection (17%), fever (7-80%)	• Labs: CBC with differential., LDH, Serum Creatinine, AST, urinalysis • Signs and Symptoms: meningococcal infection, infusion reaction • PNH (after discontinuation): signs and symptoms of hemolysis (LDH, PNH clone size or hemoglobin, fatigue, hemoglobinuria, abdominal pain, shortness of breath, thrombosis, dysphagia, erectile dysfunction • aHUS (after discontinuation): thrombotic microangiopathy complications (angina, dyspnea, mental status change, seizure or thrombosis), serum creatinine, LDH, platelets	Meningococcal infection awareness Prescriber enrollment in Soliris Risk Evaluation & Mitigation Strategy (REMS) program
Ultomiris IV (ravulizunab-cwvz)	• Central Nervous System: headache (9-32%) • Gastrointestinal: Diarrhea (4-15%) • Respiratory: upper respiratory infection (8-39%)	• PNH (after discontinuation): signs and symptoms of hemolysis (LDH, PNH clone size or hemoglobin, fatigue, hemoglobinuria, abdominal pain, shortness of breath, thrombosis, dysphagia, erectile dysfunction • aHUS (after discontinuation): thrombotic microangiopathy complications (angina, dyspnea, mental status change, seizure or thrombosis), serum creatinine, LDH, platelets • Signs and Symptoms: meningococcal infection, infusion reaction	Meningococcal infection awareness Prescriber enrollment in Ultomiris Risk Evaluation & Mitigation Strategy (REMS) program

Drug	Adverse Reactions	Monitoring	REMS
Empaveli subcutaneous (pegcetaco-plan SQ)	• Gastrointestinal: abdominal pain (20%), diarrhea (22%) • Infection: infection (29% [5% serious infection]), viral infection (12%) • Local: injection site reaction (39%) • Nervous System: fatigue (12%) • Respiratory: respiratory tract infection (15%)	• Labs: lactate dehydrogenase pre, periodically and 2 times weekly for 4 weeks after dose change • Pregnancy status prior to use in patients who may become pregnant • Signs and Symptoms: infections and hypersensitivity reaction • Hemolysis and other PBH symptoms 8 weeks post	Medication Guide, elements to assure safe uses and implementation system https://www.empavelirems.com/#Main

PNH: Paroxysmal nocturnal hemoglobinuria, aHUS: atypical hemolytic uremic syndrome, LDH: lactate dehydrogenase