Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of complement inhibitors. Agents addressed in this clinical criteria document include:

- Soliris (eculizumab)
- Ultomiris (ravulizumab-cwvz)
- Piasky (crovalimab-akkz)
- BKEMV (eculizumab-aeeb)

Eculizumab products (Soliris and interchangeable biosimilar BKEMV), Ultomiris (ravulizumab-cwvz), and Piasky (crovalimab-akkz) are monoclonal antibodies that binds to complement protein C5 and inhibits its enzymatic cleavage and blocks formation of the terminal complement complex thereby preventing red cell lysis in PNH and complement-mediated thrombotic microangiopathy in aHUS. Soliris and Ultomiris are approved for the treatment of individuals with paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG). Soliris and Ultomiris are also approved for neuromyelitis optica spectrum disorder (NMOSD). Piasky (crovalimab-akkz) is only approved for PNH, and BKEMV (eculizumab-aeeb) is approved for PNH and aHUS.

Background Information

Paroxysmal Nocturnal Hemoglobinuria (PNH): PNH is a rare acquired hematopoietic stem cell disorder associated with a variety of nonspecific clinical features including but not limited to hemolytic anemia, fatigue, smooth muscle dystonia, and atypical venous thrombosis. Treatment options are limited but may include the use of therapeutic anticoagulation, allogeneic hematopoietic cell transplantation and/or complement inhibitors (Soliris, Ultomiris, Piasky, and BKEMVi) depending upon symptom severity, degree of hemolysis, and history of thrombosis. Anti-complement therapy is used to reduce intravascular hemolysis, decrease or eliminate the need for blood transfusions, and reduce the risk for thrombosis. If Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), Piaski (crovalimab-akkz), and BKEMV (eculizumab-aeeb) therapy is discontinued, individuals should be closely monitored for at least 8 weeks after cessation to detect hemolysis.

Atypical Hemolytic Uremic Syndrome (aHUS): aHUS is a rare blood disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Treatment options are limited and include plasma therapy (plasma exchange or fresh frozen plasma infusion), renal transplantation, or complement

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

inhibitors. The efficacy of Soliris (and it's biosimilar interchangeable BKEMV) and Ultomiris in aHUS is based on their ability to inhibit complement-mediated thrombotic microangiopathy (TMA) and thereby improve renal function. If discontinued, close monitoring after cessation of therapy is essential (for example: regular laboratory monitoring including complete blood count, peripheral smear, lactate dehydrogenase, renal function, and urine protein beginning the week of the held dose and weekly for 4 weeks, every 2 weeks for 1 month, and then monthly for 3 months at the discretion of the treating clinician).

Myasthenia Gravis (MG): MG is a common disorder of neuromuscular transmission characterized by fluctuating motor weakness causing dyspnea, dysphagia, diplopia, dysarthria, and ptosis. Generalized myasthenia gravis is commonly mediated by IgG autoantibodies directed against the neuromuscular junction. Treatment strategies include symptomatic therapy (with anticholinesterase agents such as pyridostigmine), chronic immunotherapy with steroids or other immunosuppressive drugs (such as azathioprine, cyclosporine, or methotrexate), rapid immunotherapy (with plasmapheresis or IV immune globulin), and/or surgical treatment. Soliris and Ultomiris are immunotherapies which block complement activation triggered by acetylcholine receptor antibodies at the neuromuscular junction. Newer therapies, including Vyvgart, Vyvgart Hytrulo, and Rytiggo, reduce autoantibodies by binding to the neonatal Fc receptor (FcRn). Myasthenia Gravis Foundation of America (MGFA) international consensus guidelines, published prior to approval FcRn inhibitors and Ultomiris, recommend immunosuppressive drugs and/or corticosteroids for individuals who have not met treatment goals after an adequate trial of pyridostigmine. Guidelines state that Soliris may be considered in the treatment of severe, refractory MG after trials of other immunotherapies have been unsuccessful.

Neuromyelitis optica spectrum disorder (NMOSD): NMOSD is a severe autoimmune disease of the central nervous system caused by immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. This damage is triggered by antibodies against aquaporin-4 (AQP4), which are considered diagnostic criteria for NMOSD. The disease is characterized by clusters of attacks of optic neuritis or transverse myelitis with partial recovery between attacks. Progressive visual impairment and paralysis may be caused by repeated attacks. Treatment may include off-label immunosuppressive therapies including rituximab, azathioprine, and mycophenolate. Soliris (eculizumab), Uplizna (inebilizumab), and Enspryng (satralizumab) are FDA-approved for NMOSD and have demonstrated efficacy through a relative reduction in relapse rate compared to placebo.

Complement inhibitors have black box warnings for serious meningococcal infections. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors and meningococcal infection may become rapidly life-threating or fatal if not recognized and treated early. Individuals should be immunized with meningococcal vaccines at least 2 weeks prior to initiation of therapy unless the risks of delaying therapy outweigh the risk of developing a meningococcal infection. The FDA has required the manufacturers to develop comprehensive risk management programs that include the enrollment of prescribers in the Soliris REMS or Ultomiris REMS Programs respectively. Additional information and forms for individuals, prescribers, and pharmacists may be found on the manufacturer's websites: http://www.solirisrems.com or http://www.ultomirisrems.com, or www.piaskyrems.com

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

Interchangeable Biosimilars

An interchangeable biosimilar is a type of biosimilar that meets additional regulatory criteria, allowing it to be substituted for the reference product without the need for prescriber approval. This substitution can take place at the pharmacy level, depending on state-specific pharmacy regulations. All biological products undergo a stringent FDA approval process, ensuring that both biosimilars and interchangeable biosimilars provide the same level of safety and effectiveness as the original reference product

In May 2024, the FDA approved BKEMV (eculizumab-aeeb) as the first interchangeable biosimilar to Soliris (eculizumab). As an interchangeable biosimilar, BKEMV is highly similar to Soliris in terms of its composition, with no clinically significant differences. BKEMV shares the same safety warnings as Soliris and is anticipated to have comparable safety profile.

Approved Indications

Drug	Paroxysmal Nocturnal Hemoglobinuria (PNH)	Atypical Hemolytic Uremic Syndrome (aHUS)	Myasthenia Gravis (MG)	Neuromyelitis optica spectrum disorder (NMOSD)
Soliris (eculizumab)	**X**	**X**	**X**	**X**
Ultomiris (ravulizumab-cwvz)	**X**	**X**	**X**	**X**
Piasky (crovalimab-akkz)	**X**			
BKEMV (eculizumab-aeeb)	**X**	**X**		

Other Uses

A. N/A

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J1300	Injection, eculizumab, 10 mg [Soliris]
J1303	Injection, ravulizumab-cwvz, 10 mg [Ultomiris]
J3590	Unclassified biologics [when specified as Piasky, or Bkev)

ICD-10	Description
ICD-10	*Including, but not limited to, the following and any associated symptoms or complications:*
D59.3	Hemolytic-uremic syndrome [when specified as aHUS]
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
G36.0	Neuromyelitis optica [Devic]
G70.00-G70.01	Myasthenia gravis

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Clinical *Criteria: Piasky, Soliris, BKEMV, and Ultomiris*

A. Criteria For Initial Approval

Piasky (crovalimab-akkz)

Requests for initiation of therapy with Piasky (crovalimab-akkz) may be approved if the following criteria are met:

i. Individual is 13 years of age or older weighing at least 40 kg; **AND**

ii. Individual has PNH as verified by flow cytometry, including the presence of (Parker 2005):
   a. PNH type III red cell clone or a measurable granulocyte or monocyte clone; **OR**
   b. Glycosylphosphatidylinositol-anchored proteins (GPI-AP)-deficient polymorphonuclear cells (PMNs);

AND

iii. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Piasky, unless the risks of delaying Piasky outweigh the risk of meningococcal infection;

AND

iv. One of the following applies:
   a. Individual is complement inhibitor treatment naïve (i.e. not switching from eculizumab or ravulizumab) (NCT04434092);

   AND

      1. Lactate dehydrogenase greater than or equal to 2 times the upper limit of normal, and documentation is provided; **AND**
      2. One or more PNH-related sign or symptom (such as but not limited to anemia, history of major adverse vascular event from thromboembolism, or history of transfusion due to PNH);

   OR

   b. Documentation is provided that individual is switching from treatment with eculizumab or ravulizumab (NCT04432584); **AND**
   c. Treatment with eculizumab or ravulizumab will be discontinued prior to crovalimab initiation**.**

Policy Name	Policy Number	Scope	
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA	☒ MMM Multihealth

Soliris (eculizumab) and BKEMV (eculizumab-aeeb)

Requests for initiation of therapy with Soliris (eculizumab) and BKEMV (eculizumab-aeeb) in paroxysmal nocturnal hemoglobinuria (PNH) may be approved if the following criteria are met:

i. Individual is 18 years of age or older; **AND**

ii. Individual has PNH as confirmed by flow cytometry, including the presence of (Parker 2005):
   a. PNH type III red cell clone or a measurable granulocyte or monocyte clone; OR
   b. Glycosylphosphatidylinositol-anchored proteins (GPI-AP)-deficient polymorphonuclear cells (PMNs);

AND

iii. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Soliris (eculizumab), unless the risks of delaying Soliris (eculizumab) outweigh the risk of meningococcal infection;

AND

iv. Individual has (Hillmen 2006):
   a. Lactate dehydrogenase greater than 1.5 times the upper limit of normal, and documentation is provided; **AND**
   b. One or more PNH-related sign or symptom (such as but not limited to anemia or history of a major adverse vascular event from thromboembolism, or history of transfusion due to PNH).

Requests for initiation of therapy with Soliris (eculizumab) in neuromyelitis optica spectrum disorder (NMOSD) may be approved if the following criteria are met:

i. Individual is 18 years of age or older with NMOSD; **AND**

ii. Documentation is provided that NMOSD is seropositive as confirmed by the presence of anti-aquaporin-4 (AQP4) antibodies;

AND

iii. Documentation is provided that individual has a history of at least 2 acute attacks or relapses in the last 12 months prior to initiation of therapy; **OR**

iv. Documentation is provided that individual has a history of at least 3 acute attacks or relapses in the last 24 months AND at least 1 relapse in the 12 months prior to initiation of therapy;

AND

v. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Soliris (eculizumab), unless the risks of delaying Soliris (eculizumab) outweigh the risk of meningococcal infection.

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

Requests for initiation of therapy with Soliris (eculizumab) and BKEMV (eculizumab-aeeb) in <u>atypical hemolytic uremic syndrome (aHUS)</u> may be approved if the following criteria are met:

i. Individual is 2 months of age or older with a diagnosis of aHUS; **AND**
ii. The diagnosis of aHUS is supported by the absence of Shiga toxin-producing E. coli infection; **AND**
iii. Thrombotic thrombocytopenic purpura has been ruled out [for example, normal ADAMTS 13 activity and no evidence of an ADAMTS 13 inhibitor (Loirat 2011, 2016)], or if thrombotic thrombocytopenic purpura cannot be ruled out by laboratory and clinical evaluation, a trial of plasma exchange did not result in clinical improvement; **AND**
iv. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Soliris (eculizumab), unless the risks of delaying Soliris (eculizumab) outweigh the risk of meningococcal infection.

Requests for initiation of therapy with Soliris (eculizumab) in <u>generalized myasthenia gravis (gMG)</u> may be approved if the following criteria are met:

i. Individual is 18 years of age or older with gMG; **AND**
ii. Individual has Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV disease; **AND**
iii. Documentation is provided that individual has a positive serologic test for binding anti-acetylcholine receptor antibodies (AChR-ab); **AND**
iv. Documentation is provided that individual has a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 6 or higher;

AND

v. Documentation is provided that individual meets both of the following (a and b):
   a. Individual has had a trial and inadequate response or intolerance to an acetylcholinesterase inhibitor; **OR**
      i. Individual is on a stable dose of an acetylcholinesterase inhibitor; **OR**
      ii. Individual has a contraindication to acetylcholinesterase inhibitors;

   AND

   b. Individual has had a trial and inadequate response or intolerance to one or more immunosuppressive agents (including but not limited to systemic corticosteroids or non-steroidal immunosuppressants); **OR**
      i. Individual is on a stable dose of one or more immunosuppressive agents (including but not limited to systemic corticosteroids or non-steroidal immunosuppressants); **OR**
      ii. Individual has a contraindication to systemic corticosteroids and non-steroidal immunosuppressants;

AND

vi. Individual has been completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Soliris

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

(eculizumab), unless the risks of delaying Soliris (eculizumab) outweigh the risk of meningococcal infection

Ultomiris (ravulizumab-cwvz)

Requests for initiation of therapy with Ultomiris (ravulizumab-cwvz) in paroxysmal nocturnal hemoglobinuria (PNH) may be approved if the following criteria are met:

i. Individual is one month of age or older; **AND**
ii. Individual has PNH as documented by flow cytometry, including the presence of (Parker 2005):
    a. PNH type III red cell clone or a measurable granulocyte or monocyte clone; **OR**
    b. Glycosylphosphatidylinositol-anchored proteins (GPI-AP)-deficient polymorphonuclear cells (PMNs);

AND

iii. Individual has been completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Ultomiris (ravulizumab-cwvz), unless the risks of delaying Ultomiris (ravulizumab-cwvz) outweigh the risk of meningococcal infection;

AND

iv. One of the following applies:

a. Individual is complement inhibitor treatment naïve (i.e. not switching from eculizumab) (Lee 2018); **AND**
    i. Lactate dehydrogenase greater than 1.5 times the upper limit of normal, and documentation is provided; **AND**
    ii. One or more PNH-related sign or symptom (such as but not limited to anemia or history of major adverse vascular event from thromboembolism);

    OR

b. Documentation is provided that individual is switching from treatment with eculizumab (Kulasekararaj 2018); **AND**
c. Treatment with eculizumab will be discontinued prior to Ultomiris initiation.

Requests for initiation of therapy with Ultomiris (ravulizumab-cwvz) in atypical hemolytic uremic syndrome (aHUS) may be approved if the following criteria are met:

i. Individual is 1 month of age or older with a diagnosis of aHUS; **AND**
ii. The diagnosis of aHUS is supported by the absence of Shiga toxin-producing E. coli infection; **AND**
iii. Thrombotic thrombocytopenic purpura has been ruled out [for example, normal ADAMTS 13 activity and no evidence of an ADAMTS 13 inhibitor (Loirat 2011, 2016)], or if thrombotic thrombocytopenic purpura cannot be ruled out by laboratory and clinical evaluation, a trial of plasma exchange did not result in clinical improvement; **AND**

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

iv. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Ultomiris (ravulizumab-cwvz), unless the risks of delaying Ultomiris (ravulizumab-cwvz) outweigh the risk of meningococcal infection.

Requests for initiation of therapy with Ultomiris (ravulizumab-cwvz) in <u>generalized myasthenia gravis (gMG)</u> may be approved if the following criteria are met:

i. Individual is 18 years of age or older with gMG; **AND**
ii. Documentation is provided that individual has a positive serologic test for binding anti-acetylcholine receptor antibodies (AChR-ab); **AND**
iii. Individual has Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV disease; **AND**
iv. Documentation is provided that individual has a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 6 or higher;

AND

v. Documentation is provided that individual meets both of the following (a and b):
   a. Individual has had a trial and inadequate response or intolerance to an acetylcholinesterase inhibitor; **OR**
      i. Individual is on a stable dose of an acetylcholinesterase inhibitor;**OR**
      ii. Individual has a contraindication to acetylcholinesterase inhibitors;

   AND

   b. Individual has had a trial and inadequate response or intolerance to one or more immunosuppressive agents (including but not limited to systemic corticosteroids or non-steroidal immunosuppressants); **OR**
      i. Individual is on a stable dose of one or more immunosuppressive agents (including but not limited to systemic corticosteroids or non-steroidal immunosuppressants); **OR**
      ii. Individual has a contraindication to systemic corticosteroids and non-steroidal immunosuppressants

AND

vi. Individual has been completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Ultomiris (ravulizumab-cwvz), unless the risks of delaying Ultomiris (ravulizumab-cwvz) outweigh the risk of meningococcal infection.

Requests for initiation of therapy with Ultomiris (ravulizumab-cwvz) in <u>neuromyelitis optica spectrum disorder (NMOSD)</u> may be approved if the following criteria are met:

i. Individual is 18 years of age or older with NMOSD; **AND**
ii. Documentation is provided that NMOSD is seropositive as verified by the presence of anti-aquaporin-4 (AQP4) antibodies;

AND

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

iii. Documentation is provided that individual has a history of at least 1 acute attack or relapse in the 12 months prior to initiation of therapy (Pittock 2023);

AND

iv. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administration of the first dose of Ultomiris (ravulizumab-cwvz), unless the risks of delaying Ultomiris (ravulizumab-cwvz) outweigh the risk of meningococcal infection.

B. Criteria For Continuation of Therapy

Piasky (crovalimab-akkz)

Continuation requests for Piasky (crovalimab-akkz) may be approved if the following criteria are met:

i. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
ii. Documentation is provided that individual has experienced a clinical response as shown by one of the following:
    a. Stabilization of hemoglobin levels; **OR**
    b. Reduction in number of transfusions required; **OR**
    c. Improvement in hemolysis (for example, normalization or decrease of LDH levels).

Soliris (eculizumab) and BKEMVI (eculizumab-aeeb)

Requests for continued use of Soliris (eculizumab) and BKEMVI (eculizumab-aeeb) in PNH may be approved if the following criteria are met:

i. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
ii. One of the following applies:
    a. Documentation is provided that individual will be starting (or has already started) therapy with Voydeya (danicopan) in combination with Soliris within the last 6 months;
    OR
    b. Documentation is provided that individual has experienced a clinical response as shown by one of the following:
        I. Stabilization of hemoglobin levels; **OR**
        II. Reduction in number of transfusions required; **OR**
        III. Improvement in hemolysis (for example, normalization or decrease of LDH levels).

Policy Name	Policy Number	Scope	
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA	☒ MMM Multihealth

Requests for continued use of Soliris (eculizumab) in NMOSD may be approved if the following criteria are met:

i. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
ii. Documentation is provided that individual has experienced a clinical response (for example, a reduction in the frequency of relapse).

Requests for continued use of Soliris (eculizumab) and BKEMV (eculizumab-aeeb) in <u>aHUS</u> may be approved if the following criteria are met:

i. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
ii. There is clinical improvement after the initial trial (for example, increased platelet count or laboratory evidence of reduced hemolysis) until an individual becomes a candidate for physician-directed cessation as evidenced by the following (Merrill 2017):
    a. Complete clinical remission has been achieved (that is, resolution of thrombocytopenia and mechanical hemolysis, and normalization or new baseline plateau of renal function) and improvement of precipitating illness is clinically apparent; **AND**
    b. Duration of clinical remission has been stable for 2 months.

Requests for resumption of Soliris (eculizumab) and BKEMV (eculizumab-aeeb) in <u>aHUS</u> may be approved if the following criteria are met (Fakhouri 2017):

i. Documentation is provided that individual experienced a relapse after discontinuation of therapy as defined by:
    a. Reduction in platelet count to less than 150,000/mm3 or greater than 25% from baseline; **OR**
    b. Mechanical hemolysis (having 2 or more features of hemoglobin less than 10 g/dL, lactate dehydrogenase greater than 2 times upper limit of normal, undetectable haptoglobin, or presence of schistocytes on smear); **OR**
    c. Acute kidney injury with serum creatinine increase greater than 15% from baseline levels.

Requests for continued use of Soliris (eculizumab) in <u>gMG</u> may be approved if the following criteria are met:

iii. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
iv. Individual has experienced a clinical response as evidenced by both of the following:

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

a. Reduction in signs or symptoms that impact daily function; **AND**
b. Documentation is provided to show at least a 2 point reduction in MG-ADL total score from baseline.

Ultomiris (ravulizumab-cwvz)

Requests for continued use of Ultomiris (ravulizumab-cwvz) in PNH may be approved if the following criteria are met:

i. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
ii. One of the following applies:
a. Documentation is provided that individual will be starting (or has already started) therapy with Voydeya (danicopan) in combination with Ultomiris within the last 6 months; **OR**
b. Documentation is provided that individual has experienced a clinical response as shown by one of the following:
a. Stabilization of hemoglobin levels; **OR**
b. Reduction in number of transfusions required; **OR**
c. Improvement in hemolysis (for example, normalization or decrease of LDH levels).

Requests for continued use of Ultomiris (ravulizumab-cwvz) in aHUS may be approved if the following criteria are met:

i. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
ii. There is clinical improvement after the initial trial (for example, increased platelet count or laboratory evidence of reduced hemolysis) until an individual becomes a candidate for physician-directed cessation as evidenced by the following (Merrill 2017):
a. Complete clinical remission has been achieved (that is, resolution of thrombocytopenia and mechanical hemolysis, and normalization or new baseline plateau of renal function) and improvement of precipitating illness is clinically apparent; **AND**
b. Duration of clinical remission has been stable for 2 months.

Requests for resumption of Ultomiris (ravulizumab-cwvz) in aHUS may be approved if the following criteria are met (Fakhouri 2017):

i. Documentation is provided that individual experienced a relapse after discontinuation of therapy as defined by:
a. Reduction in platelet count to less than 150,000/mm3 or greater than 25% from baseline; **OR**

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

b. Mechanical hemolysis (having 2 or more features of hemoglobin less than 10 g/dL, lactate dehydrogenase greater than 2 times upper limit of normal, undetectable haptoglobin, or presence of schistocytes on smear); **OR**
c. Acute kidney injury with serum creatinine increase greater than 15% from baseline levels.

Requests for continued use of Ultomiris (ravulizumab-cwvz) in gMG may be approved if the following criteria are met:

i. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
ii. Individual has experienced a clinical response as evidenced by both of the following:
   a. Reduction in signs or symptoms that impact daily function; **AND**
   b. Documentation is provided showing at least a 2-point reduction in MG-ADL total score from baseline.

Requests for continued use of Ultomiris (ravulizumab-cwvz) in NMOSD may be approved if the following criteria are met:

i. Individual has completed or updated meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B); **AND**
ii. Documentation is provided that individual has experienced a clinical response (for example, a reduction in the frequency of relapse).

C. Authorization Duration

i. Piasky (crovalimab-akkz)
   a. Initial Approval Duration: 6 months
   b. Reauthorization Approval Duration: 6 months
ii. BKEMVI (eculizumab-aeeb)
   a. Initial Approval Duration: **PNH** 6 months
   b. Initial Approval Duration: **aHUS** 12 weeks
   c. Reauthorization Approval Duration: 6 months
iii. Soliris (eculizumab)
   a. Initial Approval Duration: **PNH** 6 months
   b. Initial Approval Duration: **NMOSD** 1 year
   c. Initial Approval Duration: **aHUS** 12 weeks
   d. Initial Approval Duration: **gMG** 26 weeks
   e. Reauthorization Approval Duration: Up to 12 months depending on clinical indications.
iv. Ultomiris (ravulizumab-cwvz)
   a. Initial Approval Duration: **PNH** 6 months
   b. Initial Approval Duration: **aHUS** 6 months

Policy Name	Policy Number	Scope	
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA	☒ MMM Multihealth

c. Initial Approval Duration: **gMG** 26 weeks
d. Initial Approval Duration: **NMOSD** 1 year
e. Reauthorization Approval Duration: Up to 12 months depending on clinical indications.

D. **Conditions Not Covered**
Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for Piasky (crovalimab-akkz) may not be approved for the following:
   a. Individual is using in combination with iptacopan, eculizumab, ravulizumab, pegcetacoplan, or danicopan; **OR**
   b. If initiating therapy, individual has evidence of an active meningococcal infection; **OR**
   c. When the above criteria (Section A) are not met and for all other indications.

ii. Requests for Soliris (eculizumab) and BVEMV (eculizumab-aeeb) may not be approved for the following:
   a. Individual is using in combination with efgartigimod alfa, ravulizumab, rituximab, inebilizumab, iptacopan, crovalimab, rozanolixizumab-noli, zilucoplan, or satralizumab; **OR**
   b. Individual is using in combination with pegcetacoplan for more than 4 weeks for PNH; **OR**
   c. If initiating therapy, individual has evidence of an active meningococcal infection; **OR**
   d. When the above criteria (Section A) are not met and for all other indications.

iii. Requests for Ultomiris (ravulizumab-cwvz) may not be approved for the following:
   a. Individual is using in combination with efgartigimod alfa, eculizumab, iptacopan, crovalimab, roozanolixizumab-noli, pegcetacoplan, or rituximab; **OR**
   b. If initiating therapy, individual has evidence of an active meningococcal infection; **OR**
   c. When the above criteria (Section A) are not met and for all other indications.

Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Piasky (crovalimab-akkz) Quantity Limit

Drug	Limit
Piasky (crovalimab-akkz) 340 mg/ 2mL (170 mg/ mL) single-dose vial*	3 vials per 28 days
Exceptions	
*Initiation of therapy: May approve 9 (nine) additional 340 mg vials in the first 29 days of treatment for a total of 12 (twelve) vials in the first 29 days of treatment; to be given as one IV loading dose [up to 1500 mg or 5 vials] on day 1 followed by SUBQ loading doses of 340 mg [1 vial] each on days 2, 8, 15, and 22. Maintenance dosing begins on day 29 and continues every 4 weeks thereafter.	

Soliris (eculizumab) and BKEMV (eculizumab-aeeb) Quantity Limit

Drug	Limit
Soliris 300 mg/30 mL vial* BKEMV 300 mg/30 mL vial*	8 vials per 28 days
Exceptions	
*Initiation of therapy for Atypical Hemolytic Uremic Syndrome (aHUS), generalized Myasthenia Gravis (MG), or neuromyelitis optica spectrum disorder (NMOSD) : May approve 4 (four) additional vials (300 mg/mL) in the first 28 days (4 weeks) of treatment. If individual receives plasma exchange [PE], plasmapheresis [PP], or fresh frozen plasma infusion during therapy, supplemental doses of Soliris (up to 600 mg following each PE or PP intervention or up to 300 mg following fresh frozen plasma) may be approved.	

Ultomiris (ravulizumab-cwvz) Quantity Limit

Drug	Limit
Ultomiris 300 mg/30 mL vial*; 300mg/3 mL vial*	12 vials per 56 days
Ultomiris 1100 mg/11 mL vial^	3 vials per 56 days
Ultomiris 245 mg/3.5 mL prefilled cartridge with on-body injector	2 cartons [with 1 prefilled cartridge and 1 on-body injector each per week
Exceptions	
Initiation of therapy: *May approve 10 (ten) additional vials (300 mg/30mL or 300mg/3mL) in the first 28 days (4 weeks) of treatment; **OR**	

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

^May approve 3 (three) additional 1100 mg vials (1100 mg/11 mL) in the first 28 days (4 weeks) of treatment.

*^If individual receives plasma exchange [PE], plasmapheresis [PP], or intravenous immunoglobulin [IVIg] interventions during therapy, supplemental intravenous doses of Ultomiris (up to 1800 mg following each PE or PP intervention or up to 600 mg following completion of an IVIg cycle) may be approved.

Reference Information

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: October 10, 2022.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINETM with AHFSTM, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
5. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006; 355(12):1233-1243.
6. Parker CJ, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005; 106(12):3699-3709.
7. Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011; 6:60.
8. Loirat C, Fakhouri F, Ariceta G, et al; HUS International. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2016; 31(1):15-39.
9. Fakhouri F, Fila M, Provot F, et al. Pathogenic variants in complement genes and risk of atypical hemolytic uremic syndrome relapse after eculizumab discontinuation. Clin J Am Soc Nephrol. 2017; 12:50-59.
10. Merrill SA, Brittingham ZD, Yuan X, et al. Eculizumab cessation in atypical hemolytic uremic syndrome. Blood. 2017; 130(3):368- 372.
11. Sanders DB, Wolfe GI, Benatar M, et al for the Task Force of the Myasthenia Gravis Foundation of America (MGFA). International consensus guidance for management of myasthenia gravis. Neurology 2016; 87:419.
12. Narayanaswami P, Sanders DB, Wolfe G, et al for the Task Force of the Myasthenia Gravis Foundation of America (MGFA). International consensus guidance for management of myasthenia gravis 2020 update. Neurology 2021; 96:114-122.
13. Lee JW, Fontbrune FS, et al. Ravulizumab vs Eculizumab in Adult Patients with PNH Naïve to Complement Inhibitors: The 301 Study. Blood 2018; prepublished online December 3, 2018; DOI 10.1182/blood-2018-09-876136.
14. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2018; Pre-published online December 3, 2018; doi: 10.1182/blood-2018-09-876805.
15. Pittock SJ, Barnett M, Bennett JL, Berthele A, de Sèze J, Levy M, Nakashima I, Oreja-Guevara C, Palace J, Paul F, Pozzilli C,

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope	
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA	☒ MMM Multihealth

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Complement Inhibitors: eculizumab agents (Soliris and biosimilar BKEMV)], Ultomiris [ravulizumab-cwvz], Piasky (crovalimab-aeeb)	MP-RX-FP-19-23	☒ MMM MA ☒ MMM Multihealth

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023
Annual Review	Add clinical criteria and quantity limit for new agents Piasky and interchangeable biosimilar BKEMV; Update PNH criteria to include age and to allow switch from other complement inhibitors; add age criteria to aHUS criteria; clarify meningococcal vaccination language, include all serogroups, and add active infection to may not approve section; Include meningococcal vaccination requirement in continuation of use criteria; Update combination exclusion statements for Ultomiris, Soliris and BKEMV; remove obsolete Ultomiris vial size; Add new indication for NMOSD to Ultomiris criteria; Update Soliris, BKEMV and Ultomiris continuation criteria in PNH to add combination use with Voydeya; wording and formatting updates. Coding Reviewed: Added HCPCS J3590 [when specified as Piasky or BKEMV]. Elevance Health's Medical Policy adoption.	9/16/2024	10/8/2024

Revised: 08/15/2024