# Medical Drug Clinical Criteria

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| **Subject:** | Complement C5 Inhibitors | | |
| **Document** #: | CC-0041 | **Publish Date**: | ~~06/12/2024~~07/29/2024 |
| **Status**: | Revised | **Last Review Date**: | ~~05/17/2024~~07/16/2024 |

## Table of Contents



## Overview

This document addresses the use of complement C5 inhibitors. Agents addressed in this clinical criteria document include:

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

Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Piasky (crovalimab-akkz) are monoclonal antibodies that bind to complement protein C5 and inhibit its enzymatic cleavage preventing formation of the terminal complement complex. 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 is also approved for neuromyelitis optica spectrum disorder (NMOSD). Piasky (crovalimab-akkz) is only approved for PNH.

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 or Ultomiris) 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), or Piasky (crovalimab-akkz) therapy is discontinued in a patient that does not switch to another treatment for PNH, individuals should be closely monitored for at least 8 weeks, 16 weeks, or 20 weeks (respectively) 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 inhibitors. The efficacy of Soliris 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).

Generalized myasthenia gravis (gMG): gMG is an autoimmune neuromuscular disorder 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), Ultomiris (ravulizumab), 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 C5 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, Ultomiris REMS, or Piasky REMS Programs respectively. Additional information and forms for individuals, prescribers, and pharmacists may be found on the manufacturer's websites: www.solirisrems.com or www.ultomirisrems.com or www.piaskyrems.com.

## Clinical Criteria

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.

**Piasky (crovalimab-akkz)**

Initial Requests for 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.

**Initial Approval Duration:** 6 months

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).

Requests for Piasky (crovalimab-akkz) may not be approved for the following:

I. Individual is using in combination with iptacopan, eculizumab, ravulizumab, pegcetacoplan, or danicopan; **OR**
II. If initiating therapy, individual has evidence of an active meningococcal infection; **OR**
III. When the above criteria are not met and for all other indications.

**Soliris (eculizumab)**

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Requests for initiation of therapy with Soliris (eculizumab) 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 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 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 or equal to 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, history of a major adverse vascular event from thromboembolism, or history of transfusion due to PNH).

**Initial Approval Duration:** 6 months

Requests for continued use of Soliris (eculizumab) 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:
        1. Stabilization of hemoglobin levels; **OR**
        2. Reduction in number of transfusions required; **OR**
        3. Improvement in hemolysis (for example, normalization or decrease of LDH levels).

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 verified 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.

**Initial Approval Duration:** 1 year

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 initiation of therapy with Soliris (eculizumab) in atypical hemolytic uremic syndrome (aHUS) 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**

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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.

**Initial Approval Duration**: 12 weeks

Requests for continued use of Soliris (eculizumab) 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 Soliris (eculizumab) 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**
    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 initiation of therapy with Soliris (eculizumab) in generalized myasthenia gravis (gMG) 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**
        1. Individual is on a stable dose of an acetylcholinesterase inhibitor; **OR**
        2. 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**
        1. Individual is on a stable dose of one or more immunosuppressive agents (including but not limited to systemic corticosteroids or non-steroidal immunosuppressants); **OR**
        2. 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 (eculizumab), unless the risks of delaying Soliris (eculizumab) outweigh the risk of meningococcal infection.

**Initial Approval Duration**: 26 weeks

Requests for continued use of Soliris (eculizumab) 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 to show at least a 2-point reduction in MG-ADL total score from baseline.

Requests for Soliris (eculizumab) may not be approved for the following:

I. Individual is using in combination with efgartigimod alfa, inebilizumab, iptacopan, crovalimab, ravulizumab, rituximab, rozanolixizumab-noli, zilucoplan, or satralizumab; **OR**
II. Individual is using in combination with pegcetacoplan for more than 4 weeks for PNH; **OR**
III. If initiating therapy, individual has evidence of an active meningococcal infection; **OR**
IV. When the above criteria are not met and for all other indications.

**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 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 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**
        1. Lactate dehydrogenase greater than 1.5 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 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.

**Initial Approval Duration:** 6 months

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:
        1. Stabilization of hemoglobin levels; **OR**
        2. Reduction in number of transfusions required; **OR**
        3. Improvement in hemolysis (for example, normalization or decrease of LDH levels).

Requests for initiation of therapy with Ultomiris (ravulizumab-cwvz) 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 verified by the presence of anti- aquaporin-4 (AQP4) antibodies;

**AND**
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.

**Initial Approval Duration:** 1 year

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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).

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**
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.

**Initial Approval Duration**: 6 months

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**
    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 initiation of therapy with Ultomiris (ravulizumab-cwvz) in generalized myasthenia gravis (gMG) 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**
        1. Individual is on a stable dose of an acetylcholinesterase inhibitor; **OR**
        2. 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**
        1. Individual is on a stable dose of one or more immunosuppressive agents (including but not limited to systemic corticosteroids or non-steroidal immunosuppressants); **OR**
        2. 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.

**Initial Approval Duration**: 26 weeks

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 Ultomiris (ravulizumab-cwvz) may not be approved for the following:

I. Individual is using in combination with eculizumab, efgartigimod alfa, iptacopan, crovalimab, pegcetacoplan, rituximab or rozanolixizumab-noli; **OR**
II. If initiating therapy, individual has evidence of an active meningococcal infection; **OR**
III. When the above criteria are not met and for all other indications.

## Step Therapy

**Note**: When Soliris for neuromyelitis optica spectrum disorder is deemed approvable based on the clinical criteria referenced above, the benefit plan may have additional criteria requiring the use of a preferred[1] agent or agents.

**Soliris for Neuromyelitis Optica Spectrum Disorder Step Therapy**

A List of preferred agents for Neuromyelitis Optica Spectrum Disorder is available here.

Requests for Solirs for neuromyelitis optica spectrum disorder may be approved when the following criteria are met:

I. Individual is stabilized on Soliris;

**OR**

II. Individual has had a trial and inadequate response or intolerance to one preferred agent:

**OR**

III. The preferred agent is not appropriate based on concomitant conditions such as infection or immunization status; **OR**
IV. Soliris may be approved for paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, or generalized myasthenia gravis.

[1]Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

## Quantity Limits

**Piasky (crovalimab-akkz) Quantity Limit**

| Drug | Limit |
|---|---|
| Piasky (crovalimab-akkz) 340 mg/ 2mL (170 mg/ mL) single-dose vial* | 3 vials per 28 days |
| **Override Criteria** | |
| *Initiation of therapy:<br>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) Quantity Limit**

| Drug | Limit |
|---|---|
| Soliris 300 mg/30 mL vial* | 8 vials per 28 days |
| **Override Criteria** | |
| *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. | |

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| 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 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 |
| **Override Criteria** | |
| Initiation of therapy:<br>*May approve 10 (ten) additional vials (300 mg/30mL or 300mg/3mL) in the first 28 days (4 weeks) of treatment.<br>^May approve 3 (three) additional 1100 mg vials (1100 mg/11 mL) in the first 28 days (4 weeks) of treatment.<br><br>*^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. | |

## Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**HCPCS**

| | |
|---|---|
| J1300 | Injection, eculizumab, 10 mg [Soliris] |
| J1303 | Injection, ravulizumab-cwvz, 10 mg [Ultomiris] |
| J3590 | Unclassified biologics [when specified as Piasky] |

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**ICD-10 Diagnosis**

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|---|---|
| | *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 |

## Document History

Revised: 07/16/2024
Document History:

- 07/16/2024 – Select Review: Add clinical criteria and quantity limit for new agent Piasky; Update combination exclusion statements for Ultomiris and Soliris. Coding reviewed: Added HCPCS J3590 [when specified as Piasky].
- 05/17/2024 – Select Review: Add new indication for NMOSD to Ultomiris criteria; Update Soliris and Ultomiris continuation criteria in PNH to add combination use with Voydeya; update exclusion for active infection to apply to initiation of therapy. Coding Reviewed: No changes.
- 02/23/2024 – Select Review: Include meningococcal vaccination requirement in continuation of use criteria; update meningococcal vaccination to include all serogroups; include iptacopan combination in may not approve criteria. Coding Reviewed: No changes.
- 11/17/2023 – Annual Review: Update PNH criteria to include age and to allow switch from other complement inhibitors; add age criteria to aHUS criteria; clarify meningococcal vaccination language and move active infection to may not approve section; add may not approve for combination with zilucoplan; remove obsolete Ultomiris vial size; wording and formatting updates. Step therapy and step therapy table add. Coding Reviewed: No changes.
- 08/18/2023 – Select Review: Update prior therapy requirements to include an acetylcholinesterase inhibitor and immunosuppressant; update MG-ADL score in continuation criteria; include rozanolixizumab in combination exclusion. Coding Reviewed: No changes.

- 11/18/2022 – Annual Review: Update combination exclusion criteria to include efgartigimod alfa; update Soliris quantity limit to include override for supplemental dosing; update Ultomiris quantity limit to include subcutaneous dosage form. Coding Reviewed: No changes.
- 06/13/2022 – Select Review: Update clinical criteria for Ultomiris to include new indication in generalized myasthenia gravis and include information about supplemental dosing in Ultomiris quantity limit; wording and formatting updates. Administrative update to add documentation. Coding Reviewed: No changes.
- 11/19/2021 – Annual Review: Clarify acute attack or relapse criteria for NMOSD; add may not be approved criteria for combination use with certain other biologics. Coding reviewed: No changes.
- 08/01/2021 – Administrative update to add documentation.
- 11/20/2020 – Annual Review: Add additional objective measures of disease severity and clinical response to myasthenia gravis indication criteria; wording and formatting updates for consistency; add new vial concentration to quantity limit for Ultomiris. Coding Reviewed: No changes.
- 11/15/2019 – Annual Review: Add continuation of use criteria for PNH; include approval duration in NMOSD criteria; add treatment of aHUS to Ultomiris criteria. Added ICD-10-DX: D59.3, D59.5, G36.0, G70.00-G70.01
- 08/16/2019 – Select Review: Add new FDA approved indication to Soliris criteria for neuromyelitis optica spectrum disorder and update quantity limit. Wording and formatting changes. Coding Reviewed: Added HCPCS J1303 (Effective10/1/19), Deleted HCPCS code J3590, C9052 (Effective 10/1/19), Added ICD-10 G36.0.
- 06/25/2019 Coding Reviewed: Add C9052 (7/1/19), Delete C9399 (7/1/19)
- 02/22/2019 – Select Review: Rename Soliris Clinical Criteria document to Complement Inhibitors Clinical Criteria document. Add new criteria for Ultomiris. Update Soliris PNH criteria for consistency. Add new step therapy for Soliris. Add new quantity limit for Ultomiris.
- 11/16/2018 – Annual Review: Initial P&T review of Soliris Clinical Guideline. Update PNH diagnostic criteria to include a measurable granulocyte or monocyte clone or type III red cell clone for clarity. Change initial approval duration for aHUS from 6 weeks to 12 weeks to allow for an adequate trial. Wording and formatting changes to criteria for clarity. HCPCS ICD-10 Coding Review: Added C9399 and J3590 for Ultomiris.

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**CC-0041 Compliment Inhibitors**

**Commercial**

| Effective Date | Preferred Agents | Non-Preferred Agents |
|---|---|---|
| N/A | N/A | N/A |

**Medicaid**

| **Effective Date** | **Preferred Agents** | **Non-Preferred Agents** |
|---|---|---|
| 06/01/2023: DC<br><br>01/01/2024: GA, MD, NY, SC, WNY, NJ | Enspryng<br>Uplizna | Soliris |

**Medicare**

| Effective Date | Preferred Agents | Non-Preferred Agents |
|---|---|---|
| N/A | N/A | N/A |