Medical Policy Bulletin
Title:
Eculizumab (Soliris®) and Related Biosimilars, Ravulizumab-cwvz (Ultomiris™) for intravenous administration
Policy #:
MA08.044k

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

ECULIZUMAB (SOLIRIS®) AND RELATED BIOSIMILARS
Eculizumab (Soliris) and related biosimilars, the Company's non-preferred products for PNH, are considered medically necessary and, therefore, covered for the treatment of PNH in adult individuals, when all of the following criteria are met, including dosing and frequency:

Initial Criteria

- The coverage will be provided for eculizumab (Soliris) and related biosimilars when one of the following is present:
  - There is a documented contraindication or documented nonresponse to ravulizumab-cwvz (Ultomiris).
  - The individual is currently receiving or has previously received a non-preferred product (e.g., eculizumab [Soliris]). (See COMPANY-DESIGNATED PREFERRED PRODUCTS and NON-PREFERRED PRODUCTS sections below).
- Flow cytometry demonstrates one of the following:
  - At least 10% PNH type III red cells
  - Greater than 50% of glycosylphosphatidylinositol-anchored proteins (GPI-AP)–deficient polymorphonuclear (PM) cells
- The individual is transfusion dependent due to PNH.
- The individual has platelet counts of at least 100,000 per cubic millimeter.
- The individual does not have unresolved *Neisseria meningitidis* infection.

- The individual is vaccinated against *N. meningitidis,* unless risk of delaying eculizumab (Soliris) outweighs risks of developing meningococcal infection.
- Dosing and frequency for eculizumab (Soliris) and related biosimilars: initial dose, 600 mg by intravenous (IV) infusion weekly for 4 weeks; maintenance, 900 mg for the fifth dose 1 week later, and then 900 mg every 2 weeks thereafter.

Continuation Criteria

Eculizumab (Soliris) and related biosimilars are considered medically necessary and, therefore, covered for continuation therapy, when documentation is provided of positive clinical response (e.g., reduction in hemolysis manifested by stabilization of hemoglobin levels and reduction in transfusions from baseline at initiation).

RAVULIZUMAB-CWVZ (ULTOMIRIS)
Ravulizumab-cwvz (Ultomiris) is considered medically necessary and, therefore, covered for adult and pediatric individuals 1 month of age or older with PNH when all of the following criteria are met, including dosing and frequency:

Initial Criteria

- The individual has a diagnosis of PNH confirmed by high-sensitivity flow cytometry of red and white blood cells with granulocyte or monocyte clone size of at least 5%.
- The individual has lactate dehydrogenase (LDH) level ≥1.5 × upper normal limit (UNL) (adult: 100 to 190 units/L at 37°C) at initiation of the therapy.
- The individual does not have history of bone marrow transplantation.
- The individual does not have unresolved *N. meningitidis* infection.
- The individual is vaccinated against *N. meningitidis,* unless risk of delaying ravulizumab-cwvz (Ultomiris) outweighs risks of developing meningococcal infection.
- Dosing and frequency for intravenous ravulizumab-cwvz (Ultomiris):
    - 5 kg to <10 kg: loading dose, 600 mg; maintenance dose, 300 mg every 4 weeks
    - 10 kg to <20 kg: loading dose, 600 mg; maintenance dose, 600 mg every 4 weeks
    - 20 kg to <30 kg: loading dose, 900 mg; maintenance dose, 2100 mg every 8 weeks
    - 30 kg to <40 kg: loading dose, 1200 mg; maintenance dose, 2700 mg every 8 weeks
    - 40 kg to <60 kg: loading dose, 2400 mg; maintenance dose, 3000 mg every 8 weeks
    - 60 kg to <100 kg: loading dose, 2700 mg; maintenance dose, 3300 mg every 8 weeks
    - ≥100 kg: loading dose, 3000 mg; maintenance dose, 3600 mg every 8 weeks

Continuation Criteria (After 26 Weeks of Therapy)

Ravulizumab-cwvz (Ultomiris) is considered medically necessary and, therefore, covered for continuation therapy following at least 26 weeks of therapy for the treatment of PNH, when documentation is provided of positive clinical response (e.g., reduction in hemolysis manifested by a stabilization of hemoglobin levels and reduction in transfusions from baseline at initiation).

ATYPICAL HEMOLYTIC–UREMIC SYNDROME (aHUS)

ECULIZUMAB (SOLIRIS) AND RELATED BIOSIMILARS
Eculizumab (Soliris) and related biosimilars, the Company's non-preferred products for aHUS, are considered medically necessary and, therefore, covered for the treatment of pediatric and adult individuals with aHUS, when all of the following criteria are met, including dosing and frequency:

Initial Criteria

- The coverage will be provided for eculizumab (Soliris) and related biosimilars, when one of the following is present:
    - There is a documented contraindication or documented nonresponse to ravulizumab-cwvz (Ultomiris)
    - The individual is currently receiving or has previously received a non-preferred product (e.g., eculizumab [Soliris]). (See COMPANY-DESIGNATED PREFERRED PRODUCTS and NON-PREFERRED PRODUCTS sections below).

- Diagnosis of thrombocytopenic purpura (TTP) has been excluded (for example, normal ADAMTS13 activity, or ADAMTS13 activity <5%) OR a trial of plasma exchange did not result in clinical improvement.
- The individual does not have unresolved *N. meningitidis* infection.
- The individual is vaccinated against *N. meningitidis,* unless risk of delaying eclizumab (Soliris) outweighs risks of developing meningococcal infection.
- The individual has an absence of Shiga toxin–producing *Escherichia coli* infection.
- Dosing and frequency for eculizumab (Soliris) and related biosimilars for adult individuals: initial, 900 mg by IV infusion weekly for 4 weeks; maintenance, 1200 mg for the fifth dose 1 week later, and then 1200 mg every 2 weeks thereafter.
- Dosing and frequency for eculizumab (Soliris) and related biosimilars for infants ≥2 months, children, and adolescents:
    - 5 kg to <10 kg: Induction: 300 mg weekly for one dose; maintenance, 300 mg at week 2, then 300 mg every 3 weeks
    - 10 kg to <20 kg: Induction: 600 mg weekly for one dose; maintenance, 300 mg at week 2, then 300 mg every 2 weeks
    - 20 kg to <30 kg: Induction: 600 mg weekly for two doses; maintenance, 600 mg at week 3, then 600 mg every 2 weeks
    - 30 kg to <40 kg: Induction: 600 mg weekly for two doses; maintenance, 900 mg at week 3, then 900 mg every 2 weeks
    - ≥40 kg: Induction: 900 mg weekly for four doses; maintenance: 1200 mg at week 5, then 1200 mg every 2 weeks
- Supplemental dosing for individuals receiving plasmapheresis or plasma exchange for adults and pediatric individuals:
    - If most recent dose was 300 mg, dose is 300 mg within 60 minutes after each plasmapheresis or plasma exchange. If most recent dose was ≥600 mg, dose is 600 mg within 60 minutes after each plasmapheresis or plasma exchange.
- Supplemental dosing for adult and pediatric individuals receiving fresh frozen plasma infusion: If most recent dose was ≥300 mg, dose is 300 mg within 60 minutes prior to each infusion of fresh frozen plasma.

Continuation Criteria (After 26 Weeks of Therapy)

Eculizumab (Soliris) and related biosimilars are considered medically necessary and, therefore, covered for continuation therapy following at least 26 weeks of therapy for the treatment
of aHUS when documentation is provided of reduction in signs of complement-mediated thrombotic microangiopathy (TMA), including at least two of the following:

- Platelet count increase from baseline at initiation
- Hematologic normalization (maintenance of normal platelet counts and LDH levels for at least 4 weeks)
- Complete complement-mediated TMA response (hematologic normalization plus at least 25% reduction in serum creatinine from baseline for at least 4 weeks)
- TMA-event free status (absence for at least 12 weeks of a decrease in platelet count >25% from baseline, treatment with plasma exchange or plasma infusion, or new dialysis treatment)
- Reduction in the daily TMA intervention rate (defined as the number of plasma exchange or plasma infusion interventions and the number of new dialysis required per individual per day)

RAVULIZUMAB-CWVZ (ULTOMIRIS)
Ravulizumab-cwvz (Ultomiris) is considered medically necessary and, therefore, covered for adult and pediatric individuals 1 month of age and older with aHUS to inhibit complement-mediated TMA when all of the following criteria are met, including dosing and frequency:

Initial Criteria

- The individual has evidence of TMA, including low platelet count, hemolysis (breaking of red blood cells inside of blood vessels), and decreased kidney function.
- The individual does not have ADAMTS13 activity <5%.
- The individual does not have unresolved *N. meningitidis* infection.
- The individual is vaccinated against *N. meningitidis* unless risk of delaying ravulizumab-cwvz (Ultomiris) outweighs risks of developing meningococcal infection.
- The individual has an absence of Shiga toxin–producing *E. coli* infection.

- The individual does not have positive direct Coombs test.
- Dosing and frequency for intravenous ravulizumab-cwvz (Ultomiris) for adults and pediatric individuals 1 month of age and older, starting 2 weeks after the loading dose, begin maintenance doses:
    - 5 kg to <10 kg: loading dose, 600 mg; maintenance dose, 300 mg every 4 weeks
    - 10 kg to <20 kg: loading dose, 600 mg; maintenance dose, 600 mg every 4 weeks
    - 20 kg to <30 kg: loading dose, 900 mg; maintenance dose, 2100 mg every 8 weeks
    - 30 kg to <40 kg: loading dose, 1200 mg; maintenance dose, 2700 mg every 8 weeks
    - 40 kg to <60 kg: loading dose, 2400 mg; maintenance dose, 3000 mg every 8 weeks
    - 60 kg to <100 kg: loading dose 2700 mg; maintenance dose, 3300 mg every 8 weeks
    - ≥100 kg: loading dose 3,000 mg; maintenance dose, 3600 mg every 8 weeks
    - For individuals switching from eculizumab (Soliris) or related biosimilars to intravenous ravulizumab-cwvz (Ultomiris), the loading dose of intravenous ravulizumab-cwvz (Ultomiris) administered 2 weeks after the last eculizumab (Soliris) infusion or related biosimilars, and then maintenance doses once every 8 weeks or every 4 weeks (depending on body weight), starting 2 weeks after loading dose administration.
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Continuation Criteria (After 26 Weeks of Therapy)

Ravulizumab-cwvz (Ultomiris) is considered medically necessary and, therefore, covered for continuation therapy, following treatment of aHUS for at least 26 weeks when there is documentation demonstrating a positive clinical response from baseline (e.g., reduction of plasma exchanges, reduction of dialysis, increased platelet count, reduction of hemolysis).

GENERALIZED MYASTHENIA GRAVIS (gMG)

ECULIZUMAB (SOLIRIS) AND RELATED BIOSIMILARS
Eculizumab (Soliris) and related biosimilars, the Company's non-preferred products for gMG, are considered medically necessary and, therefore, covered for the treatment of adult individuals with gMG, when all of the following criteria are met, including dosing and frequency:

Initial Criteria

- The coverage will be provided for eculizumab (Soliris) and related biosimilars when one of the following is present:
    - There is a documented contraindication or documented nonresponse to ravulizumab-cwvz (Ultomiris).
    - The individual is currently receiving or has previously received a non-preferred product (e.g., eculizumab [Soliris]). (See COMPANY-DESIGNATED PREFERRED PRODUCTS and NON-PREFERRED PRODUCTS sections below).
- The individual is positive for antiacetylcholine receptor (AchR) antibodies and one of the following:
    - History of abnormal neuromuscular transmission test demonstrated by SFEMG or repetitive nerve stimulation, or
    - History of positive anticholinesterase test, e.g., edrophonium chloride test, or
    - The individual has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating professional provider.
- The individual meets Myasthenia Gravis Foundation of America (MGFA) Clinical Classification* Class II to IV.
- The individual has a Myasthenia Gravis–Specific Activities of Daily Living scale (MG-ADL)** total score of six or greater.
- Documentation of prior treatments with one of the following regimens:
    - Two or more immunosuppressive agents (azathioprine [AZA], cyclophosphamide [CY], cyclosporine [CYC], mycophenolate mofetil [MMF], methotrexate [MTX], or tacrolimus [TAC]) without symptom control, or
    - One immunosuppressive therapy and chronic intravenous immunoglobulin or plasma exchange for 12 months without symptom control
- The individual does not have unresolved *N. meningitidis* infection.
- The individual is vaccinated against *N. meningitidis,* unless risk of delaying eclizumab (Soliris) outweighs risks of developing meningococcal infection.
- Dosing and frequency for eculizumab (Soliris) and related biosimilars for adults (18 and older): Initial 900 mg weekly for four doses; maintenance, 1200 mg at week 5, then 1200 mg every 2 weeks thereafter.

- Supplemental dosing for adult individuals receiving plasmapheresis or plasma exchange:
    - If the most recent dose was 300 mg, dose is 300 mg within 60 minutes after each plasmapheresis or plasma exchange. If most recent dose was ≥600 mg, dose is 600 mg, within 60 minutes after each plasmapheresis or plasma exchange.
- Supplemental dosing for adult individuals receiving fresh frozen plasma infusion: if the most recent dose was ≥300 mg, dose is 300 mg within 60 minutes prior to each infusion of fresh frozen plasma.

Continuation Criteria (After 26 Weeks of Therapy)

Eculizumab (Soliris) and related biosimilars are considered medically necessary and, therefore, covered for continuation therapy following at least 26 weeks of therapy for the treatment of gMG when documentation provided of positive clinical response (e.g., demonstration of a clinically meaningful response regarding daily activities (≥3 point improvement in the Myasthenia Gravis–Specific Activities of Daily Living scale (MG-ADL) from baseline).

RAVULIZUMAB-CWVZ (ULTOMIRIS)
Ravulizumab-cwvz (Ultomiris) is considered medically necessary and, therefore, covered for the treatment of adult individuals with gMG when all of the following criteria are met, including dosing and frequency:

Initial Criteria

- The individual is positive for AchR antibodies and one of the following:
    - History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation, or
    - History of positive anticholinesterase test, e.g., edrophonium chloride test, or
    - The individual has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating professional provider.
- The individual meets Myasthenia Gravis Foundation of America (MGFA) Clinical Classification* Class II to IV.
- The individual has an MG-ADL** total score of six or greater.
- Documentation of prior treatments with one of the following regimens:
    - Azathioprine (AZA): Must have been on AZA for ≥6 months (180 days) and have been on a stable dose for ≥2 months (60 days)
    - Immunosuppressive therapies (i.e., MMF, MTX, CYC, TAC, or CY), must have been on the immunosuppressive therapy for ≥3 months (90 days) and have been on a stable dose for ≥1 month (30 days)
    - Oral corticosteroids, must have been on a stable dose for ≥4 weeks (28 days)
    - A cholinesterase inhibitor, at the time of the screening visit, must have been on a stable dose for ≥2 weeks (14 days)
- The individual does not have unresolved *N. meningitidis* infection.
- The individual is vaccinated against *N. meningitidis,* within 3 years, or individuals who initiate ravulizumab-cwvz (Ultomiris) treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination
- Body weight ≥40 kg
- Dosing and frequency for intravenous ravulizumab-cwvz (Ultomiris) for adults (18 and older):
    - 40 kg to <60 kg: loading dose, 2400 mg; maintenance dose 3000 mg every 8 weeks
    - 60 kg to <100 kg: loading dose, 2700 mg; maintenance dose, 3300 mg every 8 weeks
    - ≥100 kg: loading dose, 3000 mg; maintenance dose, 3600 mg every 8 weeks

Continuation Criteria (After 26 Weeks of Therapy)

Ravulizumab-cwvz (Ultomiris) is considered medically necessary and, therefore, covered for continuation therapy following at least 26 weeks of therapy for the treatment of gMG when documentation provided of positive clinical response (e.g., demonstration of a clinically meaningful response regarding daily activities [≥3 point improvement in the MG-ADL from baseline]).

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

ECULIZUMAB (SOLIRIS) AND RELATED BIOSIMILARS

Eculizumab (Soliris) and related biosimilars, the Company's non-preferred products for NMOSD, are considered medically necessary and, therefore, covered for the treatment of pediatric and adult individuals with NMOSD, when all of the following criteria are met, including dosing and frequency:

Initial Criteria

- The coverage will be provided for eculizumab (Soliris) and related biosimilars when one of the following is present:
    - There is a documented contraindication or documented nonresponse to ravulizumab-cwvz (Ultomiris).
    - The individual is currently receiving or has previously received a non-preferred product (e.g., eculizumab [Soliris]). (See COMPANY-DESIGNATED PREFERRED PRODUCTS and NON-PREFERRED PRODUCTS sections below).
- The individual has diagnosis of neuromyelitis optica NMOSD.
- The individual is anti-aquaporin-4 (AQP4) antibody seropositive.
- The individual had historical relapse of at least two relapses in the last 12 months or three relapses in the last 24 months, with at least one relapse in the 12 months prior to the initiation of the therapy.
- The individual does not have unresolved *N. meningitidis* infection.
- The individual is vaccinated against *N. meningitidis*, unless risk of delaying eclizumab (Soliris) outweighs the risks of developing meningococcal infection.
- Dosing and frequency for eculizumab (Soliris) and related biosimilars for adults (18 and older):
    - 900 mg weekly for the first 4 weeks, followed by
    - 1200 mg for the fifth dose 1 week later, then
    - 1200 mg every 2 weeks thereafter.

Continuation Criteria

Eculizumab or related biosimilars are considered medically necessary for continued use in adult individuals with diagnosis of NMOSD when the initial criteria are met AND there is documentation of a positive clinical response (e.g., reductions in relapse or reduction in new onset of symptoms).

RAVULIZUMAB-CWVZ (ULTOMIRIS)

Ravulizumab-cwvz (Ultomiris) is considered medically necessary and, therefore, covered for the treatment of adult individuals with NMOSD when all of the following criteria are met, including dosing and frequency:

Initial Criteria

- The individual has diagnosis of NMOSD
- The individual is AQP4-antibody seropositive.
- The individual had at least one attack or relapse in the last 12 months prior to initiation of the therapy.
- The individual has Expanded Disability Status Scale score ≤7.
- The individual has body weight ≥40 kilograms.
- The individual does not have unresolved *N. meningitidis* infection.
- The individual is vaccinated against *N. meningitidis*, unless risk of delaying eclizumab (Soliris) outweighs the risks of developing meningococcal infection.
- Dosing and frequency for intravenous ravulizumab-cwvz (Ultomiris):
    - 40 kg to <60 kg: loading dose, 2400 mg; maintenance dose, 3000 mg every 8 weeks.
    - 60 kg to <100 kg: loading dose, 2700 mg; maintenance dose, 3300 mg every 8 weeks.
    - ≥100 kg: loading dose, 3000 mg; maintenance dose, 3600 mg every 8 weeks.

Continuation Criteria

Ravulizumab-cwvz (Ultomiris) is considered medically necessary for continued use in adult individuals with diagnosis of NMOSD when the initial criteria are met AND there is documentation of a positive clinical response (e.g., reductions in relapse or reduction in new onset of symptoms).

EXPERIMENTAL/INVESTIGATIONAL

All other uses for eculizumab (Soliris) and related biosimilars, ravulizumab-cwvz (Ultomiris), are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label

use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of eculizumab (Soliris) and related biosimilars, ravulizumab-cwvz (Ultomiris). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of eculizumab (Soliris) and related biosimilars, ravulizumab-cwvz (Ultomiris) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted eculizumab (Soliris) and related biosimilars, ravulizumab-cwvz (Ultomiris®).

REQUIRED DOCUMENTATION

Individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the service.

When coverage of eculizumab (Soliris) and related biosimilars, ravulizumab-cwvz (Ultomiris) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, eculizumab (Soliris) and related biosimilars, ravulizumab-cwvz (Ultomiris) are covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria including dosing and frequency requirements listed in this medical policy are met.

BLACK BOX WARNINGS

Refer to the specific manufacturer's prescribing information for any applicable Black Box Warnings.

Myasthenia Gravis Foundation Of America (MGFA) Clinical Classification

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.
B. 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 individual in class IVb.

MG Activities of Daily Living (MG-ADL) Profile

Grade	**Score**			
Activities of Daily Living (ADL)	**0**	**1**	**2**	**3**
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

US FOOD AND DRUG ADMINISTRATION (FDA)

Eculizumab (Soliris) was approved by the FDA on March 16, 2007, for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in order to reduce hemolysis.

Eculizumab (Soliris) was approved by the FDA on September 23, 2011, for the treatment of atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

Eculizumab (Soliris) was approved by the FDA on October 23, 2017, for the treatment of adult individuals with generalized myasthenia gravis (gMG) who are antiacetylcholine receptor (AchR) antibody positive.

Eculizumab (Soliris) was approved by the FDA on June 27, 2019, for the treatment of adult individuals with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive**.**

Ravulizumab-cwvz (Ultomiris) was approved by the FDA on December 21, 2018, for the treatment of PNH in adult individuals.

Ravulizumab-cwvz (Ultomiris) was approved by the FDA on October 19, 2019, for the treatment of aHUS to inhibit complement-mediated thrombotic microangiopathy.

Ravulizumab-cwvz (Ultomiris) was approved by the FDA on April 28, 2022, for the treatment of adult individuals with gMG who are AchR-antibody positive.

Ravulizumab-cwvz (Ultomiris) was approved by the FDA on March 25, 2024, for the treatment of adult individuals with NMOSD who are AchR-AQP4 antibody positive**.**

PEDIATRIC USE

- Use of eculizumab (Soliris) in PNH: The safety and effectiveness have not been established in the pediatric population.
- Use of eculizumab (Soliris) in aHUS: Four clinical studies assessing the safety and effectiveness of eculizumab (Soliris) for the treatment of aHUS included a total of 47 pediatric individuals (ages 2 months to 17 years). The safety and effectiveness in the pediatric population are similar to that of the adult population.
- Use of eculizumab (Soliris) in gMG. The safety and effectiveness have not been established in the pediatric population.
- Use of eculizumab (Soliris) in NMOSD. The safety and effectiveness have not been established in the pediatric population.
- Use of ravulizumab-cwvz (Ultomiris) in PNH in the pediatric population: The efficacy of ravulizumab-cwvz (Ultomiris) in pediatric individuals with PNH is similar to that observed in adult individuals with PNH enrolled in pivotal studies.
- Use of ravulizumab-cwvz (Ultomiris) in aHUS: Ongoing, multicenter, single-arm study, conducted in 16 pediatric individuals, evaluating efficacy of ravulizumab-cwvz (Ultomiris). A total of 14 eculizumab-naïve pediatric individuals (ages range, 0.9 to 17.3 years), with documented diagnosis of aHUS were enrolled and included in the interim analysis. Efficacy evaluation was based upon Complete TMA Response during the 26-week Initial Evaluation Period, which was evidenced by normalization of hematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine from baseline.
- Use of ravulizumab-cwvz (Ultomiris) in gMG: the safety and effectiveness have not been established in the pediatric population.
- Use of ravulizumab-cwvz (Ultomiris) in NMOSD: the safety and effectiveness have not been established in the pediatric population.

Description

Eculizumab (Soliris) is a first-in-class terminal complement inhibitor discovered, developed, and commercialized by Alexion Pharmaceuticals (Cheshire, CT). It has received approval from the US Food and Drug Administration (FDA) for four conditions: paroxysmal nocturnal hemoglobinuria (PNH), on March 16, 2007; atypical hemolytic–uremic syndrome (aHUS), on September 23, 2011; generalized myasthenia gravis (gMG) on October 23, 2017; and neuromyelitis optica spectrum disorder (NMOSD) on June 27, 2019. Eculizumab (Soliris) is a monoclonal antibody (mAb) that specifically binds to the complement protein with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. It is administered by intravenous infusion.

Biosimilar agents for eculizumab (Soliris) have been filed with the FDA for development. The time frame for approval is unknown.

Ravulizumab-cwvz (Ultomiris), a complement inhibitor, is a humanized mAb produced in Chinese hamster ovary (CHO) cells. Ravulizumab-cwvz is an antibody that is a terminal complement inhibitor that specifically binds with high affinity to the complement protein C5, inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing generation of the terminal complement complex C5b9. The C5 inhibition of complement-mediated hemolysis achieved by ravulizumab-cwvz in individuals with PNH is immediate, thorough, and sustained. Ravulizumab-cwvz (Ultomiris) was approved by the FDA for the treatment of PNH in adult individuals only and atypical aHUS in individuals 1 month of age and older.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

PNH is a rare condition caused by genetic mutation in the production of red blood cells (RBCs). The mutation causes RBCs to form without terminal complement inhibitors. The absence of complement inhibitors leads to the constant premature destruction and loss of RBCs (hemolysis) by the individual's own immune system. The premature loss of RBCs can result in anemia, fatigue, difficulty in functioning, dark urine, pain, shortness of breath, and blood clots.

Eculizumab (Soliris) inhibits RBC mutation and prevents intravascular hemolysis.

The safety and efficacy of eculizumab (Soliris) in individuals with PNH with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26-week study (Study 1). Individuals with PNH were also treated with eculizumab (Soliris) in a single-arm 52-week study (Study 2), and in a long-term extension study. Individuals received meningococcal vaccination prior to receipt of eculizumab (Soliris). In all studies, the dose of eculizumab (Soliris) was 600 mg every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Eculizumab (Soliris) was administered as an intravenous infusion over 25 to 45 minutes.

In Study 1, individuals with PNH with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells, and platelet counts of at least 100,000/microliter were randomly assigned to either eculizumab (Soliris) (n=43) or placebo (n=44). Prior to randomization, all individuals underwent an initial observation period to confirm the need for RBC transfusion and to identify the hemoglobin concentration (the "set-point"), which would define each individual's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in individuals with symptoms and was less than or equal to 7 g/dL in individuals without symptoms. Endpoints related to hemolysis included the numbers of individuals achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, an individual had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26-week period. Hemolysis was monitored mainly by the measurement of serum lactate dehydrogenase (LDH) levels, and the proportion of PNH RBCs was monitored by flow cytometry. Individuals receiving anticoagulants and systemic corticosteroids at baseline continued these medications. Individuals treated with eculizumab (Soliris) had significantly reduced (P<0.001) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to individuals receiving placebo. These effects were seen among individuals within each of the three pre-study RBC transfusion strata (4 to 14 units; 15 to 25 units; >25 units). After 3 weeks of eculizumab (Soliris) treatment, individuals reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of eculizumab (Soliris) on thrombotic events could not be determined.

In Study 2 and the long-term extension study, individuals with PNH with at least one transfusion in the prior 24 months and a platelet count of at least 30,000 platelets/microliter received eculizumab (Soliris) over a 52-week period. Concomitant medications included antithrombotic agents in 63% of the individuals and systemic corticosteroids in 40% of the individuals. Overall, 96 of the 97 enrolled individuals completed the study (one individual died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. A total of 187 individuals treated with eculizumab (Soliris) were enrolled in a long-term extension study. All individuals sustained a reduction in intravascular hemolysis over a total eculizumab (Soliris) exposure time ranging from 10 to 54 months. There were fewer thrombotic events with eculizumab (Soliris) treatment than during the same period of time prior to treatment. However, the majority of individuals received concomitant anticoagulants; the effect of anticoagulant withdrawal during eculizumab (Soliris) therapy was not studied.

In a study titled "A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult individuals With Paroxysmal Nocturnal Hemoglobinuria (PNH)," with primary outcome measures of normalization of LDH levels within a time frame of 26 weeks, individuals with LDH ≥1.5 times the upper limit of normal and at least one PNH symptom were randomly assigned 1:1 to receive ravulizumab or eculizumab for 183 days (N=246). Coprimary efficacy endpoints were proportion of individuals remaining transfusion-free and LDH normalization. Secondary endpoints were percent change from baseline in LDH, change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue score, proportion of individuals with breakthrough hemolysis, stabilized hemoglobin, and change in serum free C5. Ravulizumab was noninferior to eculizumab for both coprimary and all key secondary endpoints ($Pinf$ <0.0001): transfusion avoidance (73.6% vs 66.1%; difference of 6.8% [95% confidence interval [CI], −4.66–18.14]), LDH normalization (53.6% vs 49.4%, odds ratio [OR] 1.19 [0.80–1.77]), percent reduction in LDH (−76.8% vs −76.0%; difference [95% CI], −0.83% [−5.21, 3.56]), change in FACIT–Fatigue score (7.07 vs 6.40; difference [95% CI], 0.67 [−1.21−2.55]), breakthrough hemolysis (4.0% vs 10.7%; difference [95% CI], −6.7% [−14.21–0.18]), and stabilized hemoglobin (68.0% vs 64.5%; difference [95% CI], 2.9 [−8.80–14.64]). The safety and tolerability of ravulizumab and eculizumab were similar; no meningococcal infections occurred. In conclusion, ravulizumab given every 8 weeks achieved noninferiority compared with eculizumab given every 2 weeks for all efficacy endpoints, with a similar safety profile.

Ravulizumab was investigated in two large, phase 3 studies (study 301 and study 302) of PNH individuals who were either naïve to or receiving prior complement inhibitor therapy. In study 301, 246 individuals received study drug (ravulizumab, n=125; eculizumab, n=121); 195 received study drug in study 302 (ravulizumab, n=97; eculizumab, n=98). Ravulizumab met the primary objective of statistically significant noninferiority compared with eculizumab for

all primary and key secondary endpoints in both studies. Complete suppression of free C5 was attained by the end of first ravulizumab infusion (mean serum free C5 concentrations <0.5 mcg/mL) and was sustained throughout the entire 183-day treatment period for all individuals at all time points in both studies. In contrast, mean free C5 concentrations did not consistently remain less than 0.5 mcg/mL with eculizumab in either study (Panels 1 and 2). In studies 301 and 302, 15 (12.4%) and 7 (7.1%) eculizumab-treated individuals experienced one or more individual postbaseline serum free C5 level ≥0.5 mcg/mL over the 183-day treatment period.

In those studies of PNH individuals who were either naïve to or receiving prior complement inhibitor therapy, ravulizumab every 8 weeks led to immediate, complete, and sustained complement C5 inhibition in all individuals, whereas the effect of eculizumab every 2 weeks was less consistent. In individuals treated with ravulizumab, free C5 suppression below the free C5 threshold was associated with complete inhibition of intravascular hemolysis, providing a mechanistic basis for the consistency of the point estimates for all endpoints.

The pediatric study, ALXN1210-PNH-304, was a multicenter, open-label Phase 3 study conducted in eculizumab-experienced and complement inhibitor treatment-naïve pediatric individuals with PNH. All individuals received a loading dose of ravulizumab-cwvz (Ultomiris) on day 1, followed by maintenance treatment on day 15 and once every 8 weeks (q8w) thereafter (for individuals weighing ≥20 kg), or once every 4 weeks (q4w) (for individuals weighing <20 kg). For individuals who entered the study on eculizumab therapy, day 1 of study treatment was planned to occur 2 weeks from the individual's last dose of eculizumab (Soliris). The regimens of ravulizumab-cwvz provided inhibition of terminal complement in all individuals throughout the entire 26-week treatment period regardless of prior experience with eculizumab. Following initiation of ravulizumab-cwvz treatment, steady-state therapeutic serum concentrations of ravulizumab-cwvz were achieved after the first dose and maintained throughout the primary evaluation period in both cohorts. Three of five complement inhibitor treatment-naïve individuals and six of eight eculizumab experienced individuals achieved hemoglobin stabilization by Week 26, respectively. Avoidance of a transfusion was reached in 11 out of 13 individuals during the 26-week Primary Evaluation Period. One individual experienced breakthrough hemolysis during the extension period.

A clinically relevant improvement from baseline in fatigue as assessed by Pediatric FACIT–Fatigue (i.e., mean improvement of >3 units for Pediatric FACIT–Fatigue scores) was sustained throughout the primary evaluation period in the five-complement inhibitor treatment naïve individuals. A slight improvement was also observed in eculizumab-experienced individuals. However, individual-reported fatigue may be a subjective estimation, because the study was not blinded to treatment assignment. The efficacy of ravulizumab-cwvz (Ultomiris) in pediatric individuals with PNH is similar to that observed in adult individuals with PNH enrolled in pivotal studies.

ATYPICAL HEMOLYTIC–UREMIC SYNDROME

aHUS is a rare and chronic blood disease that primarily affects kidney function. This condition can occur at any age but disproportionately affects children. The syndrome causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow. aHUS is characterized by three major features related to abnormal clotting: hemolytic anemia, thrombocytopenia, and kidney failure. Studies revealed that eculizumab (Soliris) was effective in improving kidney function and platelet count in pediatric and adult individuals, and in some cases eliminated the need for dialysis.

Five single-arm studies (four prospective [aHUS Studies 1, 2, 4 and 5] and one retrospective [aHUS Study 3]) evaluated the safety and efficacy of eculizumab (Soliris) for the treatment of aHUS. Individuals with aHUS received meningococcal vaccination prior to receipt of eculizumab (Soliris) or received prophylactic treatment with antibiotics until 2 weeks after vaccination. In all studies, the dose of eculizumab (Soliris) in adults and adolescents was 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg 7 ± 2 days later, then 1200 mg every 14 ± 2 days thereafter. The dosing and frequency regimen for pediatric individuals weighing less than 40 kg enrolled in aHUS study 3 and study 5 was based on body weight. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints. Endpoints related to TMA included the following:

- Platelet count change from baseline
- Hematologic normalization (maintenance of normal platelet counts and LDH levels for at least 4 weeks)
- Complete TMA response (hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of 4 weeks)
- TMA-event free status (absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement)
- Daily TMA intervention rate (defined as the number of plasma exchange or plasma infusion interventions and the number of new dialyses required per individual per day)

aHUS Study 1 enrolled individuals who displayed signs of TMA despite receiving at least four plasma exchange/plasma infusion (PE/PI) treatments the week prior to screening. One individual had no PE/PI the week prior

to screening because of PE/PI intolerance. To qualify for enrollment, individuals were required to have a platelet count ≤150 × 109 /L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median age was 28 (range, 17–68 years). Individuals enrolled in aHUS Study 1 were required to have thrombospondin type 1 motif, member 13 (ADAMTS13) activity level above 5%; observed range of values in the trial were 70% to 121%. Seventy-six percent of individuals had an identified complement regulatory factor mutation or autoantibody. Individuals in aHUS Study 1 received eculizumab (Soliris) for a minimum of 26 weeks. In aHUS Study 1, the median duration of eculizumab (Soliris) therapy was approximately 100 weeks (range, 2 weeks to 145 weeks). Renal function, as measured by eGFR, was improved and maintained during eculizumab (Soliris) therapy. The mean eGFR (± SD) increased from 23 ± 15 mL/min/1.73m^2 at baseline to 56 ± 40 mL/min/1.73m^2 by 26 weeks; this effect was maintained through 2 years (56 ± 30 mL/min/1.73m^2). Four of the five individuals who required dialysis at baseline were able to discontinue dialysis. Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of eculizumab (Soliris). Eculizumab (Soliris) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In aHUS Study 1, mean platelet count (± SD) increased from 109 ± 32 ×109 /L at baseline to 169 ± 72 × 109 /L by 1 week; this effect was maintained through 26 weeks (210 ± 68 × 109 /L), and 2 years (205 ± 46 × 109 /L). When treatment was continued for more than 26 weeks, two additional individuals achieved hematologic normalization as well as complete TMA response. Hematologic normalization and complete TMA response were maintained by all responders. In aHUS Study 1, responses to eculizumab (Soliris) were similar in individuals with and without identified mutations in genes encoding complement regulatory factor proteins.

aHUS Study 2 enrolled individuals undergoing chronic PE/PI who generally did not display hematologic signs of ongoing TMA. All individuals had received PT at least once every 2 weeks, but no more than three times per week, for a minimum of 8 weeks prior to the first eculizumab (Soliris) dose. Individuals on chronic dialysis were permitted to enroll in aHUS Study 2. The median age was 28 years (range, 13–63 years). Individuals enrolled in aHUS Study 2 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 37% to 118%. Seventy percent of individuals had an identified complement regulatory factor mutation or autoantibody. Individuals in aHUS Study 2 received eculizumab (Soliris) for a minimum of 26 weeks. In aHUS Study 2, the median duration of eculizumab (Soliris) therapy was approximately 114 weeks (range, 26–129 weeks). Renal function, as measured by estimated glomerular filtration rate (eGFR), was maintained during eculizumab (Soliris) therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73m^2 at baseline, and was maintained through 26 weeks (37 ± 21 mL/min/1.73m^2) and 2 years (40 ± 18 mL/min/1.73m^2). No individual required new dialysis with eculizumab (Soliris). Reduction in terminal complement activity was observed in all individuals after the commencement of eculizumab (Soliris). Eculizumab (Soliris) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 × 109 /L at baseline, 233 ± 69 × 109 /L at week 26, and 224 ± 52 × 109 /L at 2 years. When treatment was continued for more than 26 weeks, six additional individuals achieved complete TMA response. Complete TMA response and hematologic normalization were maintained by all responders. In aHUS Study 2, responses to eculizumab (Soliris) were similar in individuals with and without identified mutations in genes encoding complement regulatory factor proteins.

The efficacy results for the aHUS retrospective study (aHUS Study 3) were generally consistent with results of the two prospective studies. Eculizumab (Soliris) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count (± SD) increased from 171 ± 83 × 109 /L at baseline to 233 ±109 × 109 /L after 1 week of therapy; this effect was maintained through 26 weeks (mean platelet count [± SD] at week 26: 254 ± 79 × 109 /L). A total of 19 pediatric individuals (ages 2 months to 17 years) received eculizumab (Soliris) in aHUS Study 3. The median duration of eculizumab (Soliris) therapy was 16 weeks (range, 4–70 weeks) for children 2 to less than 12 years of age (n=10), and 38 weeks (range, 1–69 weeks) for individuals 12 to less than 18 years of age (n=4). Fifty-three percent of pediatric individuals had an identified complement regulatory factor mutation or autoantibody. Overall, the efficacy results for these pediatric individuals appeared consistent with what was observed in individuals enrolled in aHUS Studies 1 and 2. No pediatric individuals required new dialysis during treatment with eculizumab (Soliris).

aHUS Study 4 enrolled individuals who displayed signs of TMA. To qualify for enrollment, individuals were required to have a platelet count less than the lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median age was 35 (range, 18–80 years). All individuals enrolled in aHUS Study 4 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 28% to 116%. Fifty-one percent of individuals had an identified complement regulatory factor mutation or autoantibody. A total of 35 individuals received PE/PI prior to eculizumab (Soliris). Individuals in aHUS Study 4 received eculizumab (Soliris) for a minimum of 26 weeks. In aHUS Study 4, the median duration of eculizumab (Soliris) therapy was approximately 50 weeks (range, 13 weeks to 86 weeks). Renal function, as measured by eGFR, was improved during eculizumab (Soliris) therapy. The mean eGFR

(± SD) increased from 17 ± 12 mL/min/1.73m^2 at baseline to 47 ± 24 mL/min/1.73m^2 by 26 weeks. Twenty of the 24 individuals who required dialysis at study baseline were able to discontinue dialysis during eculizumab (Soliris) treatment. Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of eculizumab (Soliris). Eculizumab (Soliris) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In aHUS Study 4, mean platelet count (± SD) increased from 119 ± 66 × 109 /L at baseline to 200 ± 84 × 109/L by 1 week; this effect was maintained through 26 weeks (mean platelet count [± SD] at week 26: 252 ± 70 × 109/L). In aHUS Study 4, responses to eculizumab (Soliris) were similar in individuals with and without identified mutations in genes encoding complement regulatory factor proteins or autoantibodies to factor H.

aHUS Study 5 enrolled individuals who were required to have a platelet count less than LLN, evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median age was 6.5 (range, 5 months to 17 years). Individuals enrolled in aHUS Study 5 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38% to 121%. Fifty percent of individuals had an identified complement regulatory factor mutation or autoantibody. Ten individuals received PE/PI prior to eculizumab (Soliris). Individuals in aHUS Study 5 received eculizumab (Soliris) for a minimum of 26 weeks. In aHUS Study 5, the median duration of eculizumab (Soliris) therapy was approximately 44 weeks (range, 1 dose to 88 weeks). Renal function, as measured by eGFR, was improved during eculizumab (Soliris) therapy. The mean eGFR (± SD) increased from 33 ± 30 mL/min/1.73m^2 at baseline to 98 ± 44 mL/min/1.73m^2 by 26 weeks. Among the 20 individuals with a CKD stage 2 or higher at baseline, 17 (85%) achieved a CKD improvement of stage 1 or higher. Among the 16 individuals ages 1 month to less than 12 years with a CKD stage 2 or higher at baseline, 14 (88%) achieved a CKD improvement by 1 or higher stage. Nine of the 11 individuals who required daily dialysis at study baseline were able to discontinue dialysis during eculizumab (Soliris) treatment. Responses were observed across all ages from 5 months to 17 years of age. Reduction in terminal compliment activity was observed in all individuals after commencement with eculizumab (Soliris). Eculizumab (Soliris) reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean platelet count (± SD) increased from 88 ± 42 × 109/L at baseline to 281 ± 123 x109/L by 1 week; this effect was maintained through 26 weeks (mean platelet count [±SD] at week 26: 293 ± 106 × 109/L). In aHUS Study 5, responses to eculizumab (Soliris) were similar in individuals with and without identified mutations in genes encoding complement regulatory factor proteins or autoantibodies to factor H.

Ravulizumab-cwvz (Ultomiris) was investigated in two global, single-arm, open-label studies that evaluated the efficacy of ravulizumab-cwvz in adult complement inhibitor-naïve, adolescent and pediatric individuals with aHUS**.** Study ALXN1210-aHUS-311 enrolled adult individuals and study ALXN1210-aHUS-312 enrolled pediatric (age range, 0.9–17.3 years) individuals, who displayed signs of TMA. Inclusion criteria for individuals were platelet count ≤150 × 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis, and meningococcal vaccination. In both studies, enrollment criteria excluded individuals presenting with TMA due to a disintegrin and metalloproteinase with a ADAMTS13 deficiency, Shiga toxin *Escherichia coli*–related hemolytic uremic syndrome (STEC-HUS), and genetic defect in cobalamin C metabolism. Individuals with confirmed diagnosis of STEC-HUS after enrollment were excluded from the efficacy evaluation. The ongoing pediatric study included 14 children in the interim analysis, and the adult study assessed a total of 56 individuals. The primary outcome measures for both studies was based on Complete TMA response during an initial 26-week evaluation period, defined by hematologic normalization parameters (platelet count and LDH) and improved kidney function (as measured by 25% or higher improvement in serum creatinine from baseline).

The studies demonstrated a Complete TMA Response in 71% (interim data; 95% CI, 0.42–0.92) of children and 54% (95% CI, 0.40–0.67) of adults during the initial 26-week treatment period. Other outcomes included platelet count change from baseline, dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR). Ravulizumab-cwvz treatment resulted in reduced thrombocytopenia in 93% (95% CI, 0.66–0.99) of children and 84% (95% CI, 0.72–0.92) of adults; reduced hemolysis in 86% (95% CI, 0.57–0.98) of children and 77% (95% CI, 0.64–0.87) of adults; and improved kidney function in 79% (95% CI, 0.49–0.95) of children and 59% (95% CI, 0.45–0.72) of adults. The most common adverse events were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension, and pyrexia.

GENERALIZED MYASTHENIA GRAVIS

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles. The muscle weakness usually worsens after periods of activity and improves after periods of rest. Muscles that control movements of the eye and eyelid, facial expression, chewing, talking, and swallowing are often involved, but those that control breathing and neck and limb movements may also be involved. This weakness is a result of an antibody-mediated, T-cell dependent, immunological attack directed at proteins in the postsynaptic membrane of the neuromuscular junction. MG has an annual incidence of about seven to 23 cases per million. It most often begins

before the age of 40 in women and after age 60 in men.

The efficacy of eculizumab (Soliris) for the treatment of generalized MG was established in a 26-week, randomized, double-blind, placebo-controlled, parallel group, multicenter trial (REGAIN) in 125 individuals. Among the inclusion criteria for this trial were a positive serologic test for antiacetylcholine receptor (AChR) antibodies, MG activities of daily living (MG-ADL) score of 6 or higher, and failed treatment over 1 year or more with two or more immunosuppressive therapies, or failed one immunosuppressive treatment and required chronic plasma exchange or IVIG. The primary endpoint of this trial was a change from baseline in the MG-ADL scale total score at week 26 between the placebo group and the eculizumab (Soliris) group. The MG-ADL scale is an individual-reported scale developed to assess eight typical signs and symptoms of MG and their effects on daily activities. Each item is assessed on a four-point scale in which 0 is normal function and 3 indicates loss of ability to perform that function. The change in MG-ADL score in the eculizumab (Soliris) treated group was −4.2 versus −2.3 in the placebo group. This trial narrowly missed statistical significance for the primary endpoint (*P*=0.0698); however, 18 of 22 pre-specified endpoints and analyses, based on the primary and five secondary endpoints, had results with *P* values less than 0.05 across the four assessment scales. A secondary endpoint was the change in Quantitative Myasthenia Gravis score. This is a 13-item, four-point categorical scale assessing muscle weakness from 0 (representing no weakness) to 3 (representing severe weakness). A statistically significant difference was observed in the mean change from baseline to week 26, in favor of Soliris, in total QMG scores (−4.6 in Soliris group vs −1.6 in placebo group).

The efficacy of ravulizumab-cwvz (Ultomiris) for the treatment of generalized MG was established in a randomized, double-blind, placebo-controlled, multicenter trial (ALXN1210-MG-306; NCT03920293) involving adult individuals with severe, refractory gMG and a positive serologic test for anti-AChR antibodies, MGFA clinical classification class II to IV. Inclusion criteria were a positive serologic test for AChR antibodies, MG activities of daily living (MG-ADL) score of 6 or higher. The primary efficacy endpoint was a change from baseline in the MG-ADL total score at week 26. One of the secondary endpoints was the change in the Quantitative MG total score (QMG), which is a 13-item categorical scale assessing muscle weakness. Additional secondary endpoints included the proportion of individuals with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores, respectively. Treatment with ravulizumab-cwvz (Ultomiris) demonstrated a statistically significant change in the MG-ADL and QMG total scores from baseline at week 26 in comparison to placebo. The proportion of QMG responded individuals with at least a five-point improvement at week 26 was greater for Ultomiris (30.0%) compared to placebo (11.3%); *P*=0.005. The proportion of MG-ADL responded individuals with at least a 3-point improvement at week 26 was also greater for Ultomiris (56.7%) compared to placebo (34.1%). The proportion of clinical responders at higher response thresholds (≥ four-, five-, six-, seven-, or eight-point improvement on MG-ADL, and ≥ six-, seven-, eight-, nine-, or 10-point improvement on QMG) was consistently greater for Ultomiris compared to placebo. The most common adverse reactions (incidence ≥10%) were diarrhea and upper respiratory tract infection.

NEUROMYELITIS OPTICA SPECTRUM DISORDER

NMOSD is a relapsing, autoimmune, inflammatory disorder that typically affects the optic nerves and spinal cord. At least two thirds of cases are associated with aquaporin-4 antibodies (AQP4-IgG) and complement-mediated damage to the central nervous system.

The efficacy and safety of eculizumab (Soliris) for the treatment of individuals with AQP4-IgG–positive neuromyelitis optica was evaluated in a phase 3, randomized, double-blind, placebo-controlled, time-to-event trial (PREVENT [Prevention of Relapses in Neuromyelitis Optica]). The study enrolled 143 individuals were enrolled at 70 sites, primarily hospital clinics, in 18 countries. Of the 143 patients, 46 (32%) had received rituximab previously but not within the 3 months before screening. A total of 34 patients (24%) did not receive any concomitant immunosuppressive therapy during the trial. The baseline characteristics of the patients were well balanced between the two groups.

The individuals were stratified across sites according to the score on the Expanded Disability Status Scale (EDSS) on day 1 (≤2.0 or 2.5 to 7.0 on a scale ranging from 0 [no disability] to 10 [death]) and the use of concomitant immunosuppressive therapy. The trial was designed to continue until 24 individuals had a relapse of NMOSD, as adjudicated by an independent panel.

The primary endpoint was the time to the first adjudicated on-trial relapse. An On-trial Relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persisted for more than 24 hours as confirmed by the treating physician. Secondary outcomes included the adjudicated annualized relapse rate (ARR), quality-of-life measures, and the score on the Expanded Disability Status Scale (EDSS), which ranges from 0 (no disability) to 10 (death). Adjudicated relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in the placebo group (hazard ratio, 0.06; 95% confidence interval [CI], 0.02 to 0.20; *P*<0.001). The adjudicated annualized relapse rate was 0.02 in the

eculizumab group and 0.35 in the placebo group (rate ratio, 0.04; 95% CI, 0.01 to 0.15; *P*<0.001). The mean change in the EDSS score was -0.18 in the eculizumab group and 0.12 in the placebo group (least-squares mean difference, -0.29; 95% CI, -0.59 to 0.01). Upper respiratory tract infections and headaches were more common in the eculizumab group.

The efficacy and safety of Ultomiris in adult individuals with anti-AQP4 antibody positive NMOSD was studied in an open-label multicenter protocol, Study ALXN1210- NMO-307 (NCT04291262).
Study ALXN1210-NMO-307 enrolled 58 adult individuals with NMOSD who had a positive serologic test for anti-AQP4 antibodies, at least one relapse in the last 12 months prior to the Screening Period, and an Expanded Disability Status Scale (EDSS) score of 7 or less. In the placebo control group, eligibility criteria were similar except individuals were required to have at least two relapses in last 12 months or three relapses in the last 24 months with at least one relapse in the 12 months prior to screening.

The primary endpoint of Study ALXN1210-NMO-307 was the time to first adjudicated on-trial relapse. No relapses were observed in Ultomiris-treated individuals during the Primary Treatment Period, representing a statistically significant difference between the Ultomiris and placebo treatment arms in time to first adjudicated on-trial relapse (*P*<0.0001). The hazard ratio (95% CI) for Ultomiris compared with placebo was 0.014 (0.000, 0.103), representing a 98.6% reduction in the risk of relapse. Ultomiris-treated individuals experienced similar improvement in time to first adjudicated on-trial relapse with or without concomitant treatment. Most common adverse reactions in adult individuals with NMOSD (incidence ≥10%) were COVID-19, headache, back pain, arthralgia, and urinary tract infection.

RISK EVALUATION AND MITIGATION STRATEGY

Eculizumab (Soliris) and related biosimilars, ravulizumab-cwvz (Ultomiris) were approved by the FDA with a risk evaluation and mitigation strategy (REMS) due to the risk of meningococcal infections. Under the REMS, prescribers must enroll in the program, counsel individuals about the risk of meningococcal infection, provide individuals with the REMS educational materials, and ensure that individuals are vaccinated with a meningococcal vaccine.

OFF-LABEL INDICATIONS

There may be additional indications contained in the policy section of this document due to evaluation of criteria highlighted in the company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)

ECULIZUMAB (SOLIRIS®) AND RELATED BIOSIMILARS, RAVULIZUMAB-CWVZ (ULTOMIRIS™) ARE MEDICALLY NECESSARY WHEN REPORTED WITH THE FOLLOWING DIAGNOSIS CODES:
D59.3 Hemolytic-uremic syndrome
D59.5 Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
G36.0 Neuromyelitis optica [Devic]
G70.00 Myasthenia gravis without (acute) exacerbation
G70.01 Myasthenia gravis with (acute) exacerbation

HCPCS Level II Code Number(s)

J1299 Injection, eculizumab, 2 mg

J1303 Injection, ravulizumab-cwvz, 10 mg

Q5151 Injection, eculizumab-aagh (epysqli), biosimilar, 2 mg

Q5152 Injection, eculizumab-aeeb (bkemv), biosimilar, 2 mg

Modifiers

THE FOLLOWING MODIFIER IS USED WHEN REPORTING

Eculizumab (Soliris®) and Related Biosimilars, Ravulizumab-cwvz (Ultomiris®)
JA Administered intravenously

Policy History

Revisions from MA08.044k

06/13/2025	This policy has been identified for a HCPCS code update, effective 06/13/2025. Inclusion of a policy in a Code Update memo does not imply that a full review of the policy was completed at this time. The following HCPCS codes have been added to this policy: J1299 Injection, eculizumab, 2 mg Q5151 Injection, eculizumab-aagh (epysqli), biosimilar, 2 mg Q5152 Injection, eculizumab-aeeb (bkemv), biosimilar, 2 mg The following HCPCS codes have been removed to this policy: J1300 Injection, eculizumab, 10 mg Q5139 Injection, eculizumab-aeeb (bkemv), biosimilar, 10 mg

Revisions From MA08.044j

03/28/2025	This version of the policy will become effective 03/28/2025. Inclusion of a policy in a Code Update memo does not imply that a full review of the policy was completed at this time. The following HCPCS code has been added to this policy: Q5139 Injection, eculizumab-aeeb (bkemv), biosimilar, 10 mg

Revisions From MA08.044i:

09/16/2024	This version of the policy will become effective 09/16/2024.

	This policy has been updated to communicate the medical necessity criteria, including dosing and frequency requirements, for the newly US Food and Drug Administration (FDA)-approved indication, neuromyelitis optica spectrum disorder (NMOSD), for ravulizumab-cwvz (Ultomiris). Additional medical necessity criteria including dosing and frequency requirements were included, consistent with the FDA labeling.

Revisions from MA08.044h

05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
09/05/2023	This policy has been reissued in accordance with the Company's annual review process.
03/22/2022	This policy has been reissued in accordance with the Company's annual review process.
10/17/2022	This version of the policy will become effective 10/17/2022. This policy has been updated to communicate the medical necessity criteria, including dosing and frequency requirements, for the newly FDA-approved indication of generalized myasthenia gravis (gMG) for ravulizumab-cwvz (Ultomiris™).

Revisions from MA08.044g

04/27/2022	This version of the policy will become effective 04/27/2022 This policy has been updated to communicate the medical necessity criteria, including dosing and frequency requirements, for the newly FDA-approved indication for ravulizumab-cwvz (Ultomiris™). Additional medical necessity criteria, including dosing and frequency requirements were included, consistent with the US Food and Drug Administration (FDA) labeling and requirement for laboratory testing.

Revisions from MA08.044f

05/19/2021	This policy has been reissued in accordance with the Company's annual review process
04/20/2020	This version of the policy will become effective 04/20/2020. This policy has been updated to communicate the medical necessity criteria, including dosing and frequency requirements, for the newly FDA-approved indication of neuromyelitis optica spectrum disorder (NMOSD) for eculizumab (Soliris®) and atypical hemolytic uremic syndrome (aHUS) for ravulizumab-cwvz (Ultomiris®). Additional medical necessity criteria and dosing and frequency requirements were included for eculizumab (Soliris®) and ravulizumab-cwvz (Ultomiris®), consistent with the US Food and Drug Administration (FDA) labeling and requirement for laboratory testing. Preferred agent is designated in this policy to ravulizumab-cwvz (Ultomiris®) for FDA approved indications of aHUS. The following ICD-10 code G36.0 Neuromyelitis optica [Devic] was added to this policy for eculizumab (Soliris®) and D59.3 Hemolytic-uremic syndrome for ravulizumab-cwvz (Ultomiris®).

Revisions from MA08.044e

10/01/2019	This policy has been identified for the HCPCS code update, effective 10/01/2019. The following HCPCS code has been **added** to this policy: J1303 Injection, ravulizumab-cwvz, 10 mg The following HCPCS codes have been **removed** from this policy: C9052 Injection, ravulizumab-cwvz, 10 mg J3590 Unclassified Biologics

Revisions from MA08.044d

07/01/2019	The following policy has been updated to communicate the medical necessity criteria, including dosing and frequency requirements, for the newly FDA-approved product, ravulizumab-cwvz (Ultomiris™). Additional medical necessity criteria, including dosing and frequency requirements were included for eculizumab (Soliris®), consistent with the US Food and Drug Administration (FDA) labeling and requirement for laboratory testing. ---------- **Note**: On 6/18/2019 this policy in Notification was updated to incorporate HCPCS coding changes effective 07/01/2019. The following HCPCS code was **removed**: C9399 Unclassified drugs or biologics. The following HCPCS code was **added**: C9052 Injection, ravulizumab-cwvz, 10 mg

MA08.044c

09/26/2018	This policy has been reissued in accordance with the Company's annual review process.
12/27/2017	This policy has undergone a routine review and the medical necessity criteria have been revised to reflect the United States Food and Drug Administration (FDA) labeling and National Comprehensive Cancer Network (NCCN) compendia.

MA08.044b

03/23/2016	This policy will become effective 03/23/2016. It has been updated to indicate the Company's continuing coverage position for the use of eculizumab (Soliris) for use in paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic-uremic syndrome (aHUS). The Description section was updated to include information about the clinical studies that were performed to support the FDA labeling for eculizumab (Soliris®). Additionally, information about the Risk Evaluation and Mitigation Strategy for eculizumab (Soliris®) was added. The Policy section was updated to communicate that treatment with eculizumab (Soliris®) for individuals with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS) is not indicated. This statement was included in Policy Guidelines section during previous policy iteration.

MA08.044a

01/01/2015	This policy will become effective 01/15/2015. It has been updated to indicate the Company's continuing coverage position for the use of eculizumab (Soliris) for use in paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic-uremic syndrome (aHUS). Eculizumab (Soliris®) is considered medically necessary and, therefore, covered for adults when used for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. Eculizumab (Soliris®) is considered medically necessary and, therefore, covered for individuals 2 months to 17 years, and adults, when used for the treatment of atypical hemolytic-uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

MA08.044

01/01/2015	This is a new policy.

Version Effective Date:
06/13/2025
Version Issued Date:
06/13/2025
Version Reissued Date:
N/A