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Effective Date: 10/12/2023

Ultomiris™ (ravulizumab)

HCPCS: J1303

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

- A. Coverage of the requested drug is provided when all the following are met:
 - a. FDA approved age
 - b. Documented diagnosis of paroxysmal nocturnal hemoglobinuria (PNH)
 - i. Flow cytometric confirmation of PNH type III red cells
 - ii. Had at least 1 transfusion in 24 months preceding ravulizumabOR
 - iii. Documented history of major adverse thrombotic vascular events from thromboembolismOR
 - iv. Patient has high disease activity defined as a lactic dehydrogenase (LDH) level ≥ 1.5 times the upper limit of normal with one of the following symptoms
 - 1. Weakness
 - 2. Fatigue
 - 3. Hemoglobinuria
 - 4. Abdominal pain
 - 5. Dyspnea
 - 6. Hemoglobin < 10 g/dL
 - 7. A major vascular event
 - 8. Dysphagia
 - 9. Erectile dysfunction
 - v. Must not be used in combination with Soliris®, Empaveli™, or other medications to treat PNH
- c. Documentation diagnosis of atypical hemolytic uremic syndrome (aHUS)
 - i. Common causes of typical hemolytic uremic syndrome have been ruled out, including infectious causes of HUS and thrombotic thrombocytopenic purpura (TTP)
 - ii. Must present with the following symptoms:
 - 1. Hemoglobin < 10 g/dL
 - 2. Platelets $< 150,000/mm^3$
 - 3. Documented evidence of hemolysis, such as, elevated lactate dehydrogenase levels, decreased haptoglobin level, or schistocytosis
 - 4. Increased serum creatinine OR currently undergoing dialysis

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- iii. Must not be used in combination with Soliris or other medications to treat aHUS
- d. Diagnosis of refractory generalized myasthenia gravis (MG) (IV formulation only)
 - i. Documented diagnosis of refractory, anti-acetylcholine receptor (AChR) antibody positive MG identified by:
 - 1. Lab record or chart notes identifying the patient is positive for anti-AChR antibodies AND
 - 2. One of the following confirmatory tests:
 - a) Positive edrophonium test
 - b) History of clinical response to oral cholinesterase inhibitors (for example: pyridostigmine)
 - c) Electrophysiological evidence of abnormal neuromuscular transmission by repetitive nerve stimulation (RNS) or single-fiber electromyography (SFEMG)
 - ii. Patients must NOT have a history of:
 - 1. Thymectomy within 12 months
 - 2. Current thymoma
 - 3. Other neoplasms of the thymus
 - iii. Must have class II – IV disease
 - iv. Previous treatment courses of at least 12 weeks with one of the following standards of care have been ineffective: methotrexate, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, or tacrolimus unless all are contraindicated or not tolerated
 - v. Patient is currently receiving, and will continue to receive, a stable standard of care regimen
 - vi. Must not be using with other biologic therapies for myasthenia gravis or immunoglobulin therapy
- e. For the subcutaneous self-administered formulation, patients must have received the first intravenous loading dose under the guidance of a health care provider
- f. Trial and failure, intolerance, or a contraindication to the preferred products as specified in the BCBSM/BCN medical utilization management drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria

- a. Quantity Limits: Align with FDA recommended dosing
- b. Authorization Period: One year at a time
- c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information

- Ultomiris is a complement inhibitor indicated for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy, and generalized myasthenia gravis who are anti-AChR antibody-positive. Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). The subcutaneous formulation is not indicated for use in MG.
- Paroxysmal nocturnal hemoglobinuria
 - Paroxysmal nocturnal hemoglobinuria is a rare acquired hematopoietic stem cell disorder in which red blood cells undergo cell lysis prematurely mediated by the alternative pathway of complement (APC). PNH arises

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due to a somatic mutation of a the PIGA gene whose protein product is a glycosyl transferase. Glycosyl transferase is part of the biosynthetic pathway that generates glycosyl phosphatidylinositol (GPI) that serves as an anchor for membrane bound proteins on hematopoietic lineage cells. The mutation in PIGA results in a lack of glycosyl transferase activity and near-complete or complete absence of expression of all proteins that are GPI-anchored including the complement inhibitory proteins CD55 and CD59. The deficiency of CD55 and CD59 cause the complement-mediated intravascular hemolysis characteristic of PNH.

- Phenotypic mosaicism of the peripheral blood is a characteristic feature of PNH and is based on quantitative differences in complement sensitivity. Cell complement sensitivity is divided into 3 types. PNH type I cells are defined by having normal sensitivity to complement-mediated lysis. PNH type II cells are moderately complement sensitive or 2 - 4 times more sensitive than normal. Finally, PNH type III cells are markedly complement sensitive or 15 - 25 times more sensitive than normal. Complement sensitivity varies greatly from patient to patient depending on their unique phenotypic mosaicism. Erythrocyte phenotype is clinically relevant as patients with primarily type II cells have a relatively benign clinical course. In contrast, those who have more type III cells, which are completely deficient in CD55 and CD59, will have a more severe clinical course due to increased complement-mediated hemolysis. As Ultomiris is a complement inhibitor, it was studied only in patients with greater than 5% PNH type III cells on flow cytometry.
 - For patients with high disease activity, PNH complications increase significantly. High disease activity is defined as an elevated LDH greater than or equal to 1.5 times the upper limit of normal with constitutional symptoms of weakness, fatigue, hemoglobinuria, abdominal pain, dyspnea, hemoglobin less than 10 g/dL, dysphagia, and erectile dysfunction. Patients with an elevated LDH and at least one additional symptoms should begin treatment with Ultomiris.
 - Thrombolytic complications are the leading cause of morbidity and mortality in PNH. Acute thrombotic events require anticoagulation with heparin. If there is no contraindication, anticoagulation should continue indefinitely for a patient with PNH who has experienced a thromboembolic complication. For patients being treated with Ultomiris and no history of thromboembolic complications, prophylactic anticoagulation may be unnecessary, although it is recommended that anticoagulation continue for those patients who experienced a thromboembolic event prior to initiating therapy with Ultomiris.
 - Ultomiris has been shown to decrease the number of blood transfusions required by patients and stabilize hemoglobin levels and to be non-inferior to Soliris in regards to these endpoints. Soliris has been studied in patients receiving as few on 1 blood transfusion in 24 months while the Ultomiris studies had patients averaging at least 1 blood transfusion within the 12 months prior to the trial.
 - Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat PNH, such as, Soliris.
- Atypical hemolytic uremic syndrome
- Atypical hemolytic uremic syndrome is an extremely rare disease characterized by hemolytic anemia, thrombocytopenia, and acute kidney failure. Acute presentation may also include neurological findings, including seizures, gastrointestinal symptoms, and cardiovascular involvement, including hypertensive emergency and acute coronary events. Chronic kidney disease (CKD) is the most common long-term complication and may result in the need for dialysis. The signs and symptoms of aHUS result from the formation of microthrombi in various small blood vessels of the body. These clots reduce or prevent proper blood flow to various organs especially the kidneys. Multiple factors, including certain genetic, environmental, and immunologic factors, all play a role in its development.

- The nomenclature and terminology surrounding aHUS can be confusing. Atypical hemolytic uremic syndrome is considered a form of thrombotic microangiopathy (TMA). TMA is broken down into two main forms, thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS).
 - TTP is group of syndromes in which patients usually present with thrombocytopenia and microangiopathic hemolytic anemia. Despite similarities in clinical features, the underlying mechanisms of aHUS and TTP differ, altering the manner in which patients respond to different therapies. TTP results from mutations in the gene encoding a disintegrin and metalloprotease with thrombospondin type 1 motif 13 or ADAMTS13. Patients who are severely ADAMTS13 deficient, defined as ADAMTS13 activity less than 10%, have a confirmed diagnosis of TTP and may not respond to complement-inhibitor therapy. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of TTP and therefore, Ultomiris should not be prescribed.
 - HUS is also broken down into two main forms, aHUS and secondary HUS. Secondary HUS are caused by Shiga toxin E. coli, S. pneumoniae, malignancy, HIV infection, solid organ transplants, hematopoietic stem cell transplants, autoimmune disorders and the use of certain drugs or medications. HUS caused by infectious bacteria typically presents with diarrhea and responds well to antibiotic therapy. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of infectious HUS and Soliris should not be initiated in these patients. Atypical hemolytic uremic syndrome typically results from complement abnormalities, however, it is a diagnosis of exclusion, meaning the diagnosis is made by excluding other primary thrombotic microangiopathy (TMA) syndromes, such as TTP or infectious HUS.
- Most patients with aHUS present with the complete triad symptoms: hemoglobin less than 10 g/dL, platelets less than 150,000/mm³, and renal insufficiency with increased serum creatinine or the need for dialysis. The presence of schizocytes, undetectable haptoglobin, and high LDH levels confirm the microangiopathic intravascular origin of hemolysis. Ultomiris should be initiated in patients with these symptoms and a lack of secondary or infectious causes.
- Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat aHUS, such as, Soliris.
- Myasthenia gravis
 - Myasthenia gravis is a rare autoimmune disease resulting from an immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities. Approximately 10-15% of MG cases will become refractory resulting in profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Refractory disease is defined by the 2016 international consensus guidance for management of myasthenia gravis as worsening or unchanged disease despite use of corticosteroids and at least two different immunosuppressive therapies used in adequate doses for an adequate duration with persistent symptoms and/or side-effects that limit function.
 - Soliris has only been studied and shown to be safe or effective in patients with anti-AChR antibodies. An immunologic assay to detect for the presence of anti-AChR antibodies is the first step towards a diagnosis of MG. Once it is determined a patient has anti-AChR antibodies, at least one other confirmatory test

including a positive edrophonium test, history of response to oral cholinesterase inhibitors, repetitive nerve stimulation (RNS), or single-fiber electromyography (SFEMG) should be conducted.

- The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. The 2020 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on Class II evidence from a meta-analysis. Benefit from thymectomy is usually delayed and is often only identified several years post-surgery. Also, patients with thymomas, tumors originating from the epithelial cells of the thymus, may develop MG. Guidelines state the presence of thymoma is always a surgical indication, regardless of the severity of MG, followed by chemotherapy and radiation to treat the tumor as appropriate. Soliris has not been studied in patients who have undergone thymectomy within 12 months, those with thymoma, and those with other tumors of the thymus. There is no safety and efficacy data to support use of Soliris in these patient populations at this time.
- Standard therapies recommended by the 2020 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, IVIG, and PLEX.
 - Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.
 - Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.
 - Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect and doses should be maintained for six months to two years of therapy and then tapered to the lowest effect dose.
 - Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.
 - PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX.

- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. A number of case reports and case series support the efficacy of rituximab in patients with refractory MG. In a prospective study of 22 patients with refractory MG treated with rituximab, the mean time to relapse was 17 months. Among 14 patients taking prednisone, the mean daily dose decreased from 25 mg at baseline to 7 mg after treatment with a mean follow-up of 29 months. In an observational study of 72 patients with new-onset or refractory generalized MG, those treated with low-dose rituximab had shorter time to remission, lower use of adjunctive treatments, and fewer adverse events than patients treated with conventional immunosuppressive therapy.
- Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat MG, such as, Soliris, or one medication is superior to the other.

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Policy History												
#	Date	Change Description										
2.0	Effective Date: 10/12/2023	Annual review – no changes to criteria at this time										
1.9	Effective Date: 10/06/2022	Updated to include the new subcutaneous formulation										
1.8	Effective Date: 06/09/2022	Updated to include new indication of myasthenia gravis and remove prescriber requirements										
1.7	Effective Date: 06/10/2021	Update to remove platelet requirement for PNH and the percentage of PNH type III cells required										
1.6	Effective Date: 12/03/2020	Updated to remove meningitis vaccine criteria, added prescriber for PNH and aHUS diagnoses, added requirement to rule out typical hemolytic uremic syndrome, added trial and failure of preferred products statement, and changed renewal criteria to general standard statement.										
1.5	Effective Date: 12/05/2019	Updated to add new indication of aHUS										
1.4	Effective Date: 08/15/2019	Updated criteria to exclude combination use with Soliris										
1.3	Effective Date: 06/03/2019	UM medical management system update for MAPPO and BCNA <table border="1" data-bbox="483 814 1365 1024"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>Yes</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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1.2	Effective Date: 05/01/2019	UM medical management system update for BCBSM <table border="1" data-bbox="483 1100 1365 1310"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>TBD</td> </tr> <tr> <td>BCNA</td> <td>TBD</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	TBD	BCNA	TBD
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1.0	Effective Date: 02/14/2019	<p data-bbox="462 136 592 168">New Policy</p> <table border="1" data-bbox="483 199 1365 409"> <thead> <tr> <th data-bbox="483 199 963 268">Line of Business</th> <th data-bbox="963 199 1365 268">PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td data-bbox="483 268 963 304">BCBS</td> <td data-bbox="963 268 1365 304">No</td> </tr> <tr> <td data-bbox="483 304 963 340">BCN</td> <td data-bbox="963 304 1365 340">No</td> </tr> <tr> <td data-bbox="483 340 963 375">MAPPO</td> <td data-bbox="963 340 1365 375">TBD</td> </tr> <tr> <td data-bbox="483 375 963 409">BCNA</td> <td data-bbox="963 375 1365 409">TBD</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	No	MAPPO	TBD	BCNA	TBD
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website o <http://dailymed.nlm.nih.gov/dailymed/index.cfm>*