Ultomiris (ravulizumab-cwvz)

Override(s)	Approval Duration
Prior Authorization	1 year except as noted within the criteria below

Medications	Quantity Limit
Ultomiris (ravulizumab-cwvz) 300 mg/3 mL vial*	12 vials per 56 days
Ultomiris (ravulizumab-cwvz) 1100 mg/11 mL vial^	3 vials per 56 days
Ultomiris (ravulizumab-cwvz) 245 mg/3.5 mL prefilled cartridge with on-body injector	2 cartons [with 1 prefilled cartridge and 1 on-body injector each] per week

Initiation of therapy:
*May approve 10 (ten) additional 300 mg vials (300 mg/3mL) in the first 28 days (4 weeks) of treatment.
^May approve 3 (three) additional 1100 mg vials (1100 mg/11 mL) in the first 28 days (4 weeks) of treatment.

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

APPROVAL CRITERIA

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

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

AND
III. Individual has been completed or updated meningococcal vaccination at least 2 weeks prior to administration of the first dose of Ultomiris (ravulizumab-cwvz), the risks of delaying Ultomiris (ravulizumab-cwvz) outweigh the risk of meningococcal infection;

AND

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

   OR

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

Initial Approval Duration: 6 months

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

I. Documentation is provided that individual has experienced a clinical response as shown by one of the following:
   A. Stabilization of hemoglobin levels; **OR**
   B. Reduction in number of transfusions required; **OR**
   C. Improvement in hemolysis (for example, normalization or decrease of LDH levels).

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

I. Individual is 1 month of age or older with a diagnosis of aHUS;

AND

II. The diagnosis of aHUS is supported by the absence of Shiga toxin-producing E. coli infection;

AND

III. Thrombotic thrombocytopenic purpura has been ruled out [for example, normal ADAMTS 13 activity and no evidence of an ADAMTS 13 inhibitor (Loirat 2011, 2016)], or if thrombotic thrombocytopenic purpura cannot be ruled out by laboratory and clinical evaluation, a trial of plasma exchange did not result in clinical improvement;

AND

IV. Individual has completed or updated meningococcal vaccination at least 2 weeks prior to administration of the first dose of Ultomiris (ravulizumab-cwvz), unless the risks of delaying Ultomiris (ravulizumab-cwvz) outweigh the risk of meningococcal infection.

Initial Approval Duration: 6 months

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

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

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

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

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

I. Individual is 18 years of age or older with gMG;

AND

II. Documentation is provided that individual has a positive serologic test for binding anti-acetylcholine receptor antibodies (AChR-ab);

AND

III. Individual has Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV disease;

AND

IV. Documentation is provided that individual has a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 6 or higher;

AND

V. Documentation is provided that individual meets both of the following (A and B):
   A. Individual has had a trial and inadequate response or intolerance to an acetylcholinesterase inhibitor; **OR**

1. Individual is on a stable dose of an acetylcholinesterase inhibitor; **OR**
2. Individual has a contraindication to acetylcholinesterase inhibitors;

AND

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

AND

VI. Individual has been completed or updated meningococcal vaccination at least 2 weeks prior to administration of the first dose of Ultomiris (ravulizumab-cwvz), unless the risks of delaying Ultomiris (ravulizumab-cwvz) outweigh the risk of meningococcal infection.

Initial Approval Duration: 26 weeks

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

I. Individual has experienced a clinical response as evidenced by both of the following:
    A. Reduction in signs or symptoms that impact daily function; **AND**
    B. Documentation is provided showing at least a 2-point reduction in MG-ADL total score from baseline.

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

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

Note:
Ultomiris (ravulizumab-cwvz) has a black box warnings for serious meningococcal infections. Life-threatening and fatal meningococcal infections have occurred in patients treated with Ultomiris (ravulizumab-cwvz) and meningococcal infection may become rapidly life-threating or fatal if not recognized and treated early. Individuals should be immunized with meningococcal vaccines at least 2 weeks prior to initiation of therapy unless the risks of delaying therapy outweigh the risk of developing a meningococcal infection. The FDA has required the manufacturer to develop comprehensive risk management programs that includes the enrollment of prescribers in the Ultomiris REMS Program. Additional information and forms for

individuals, prescribers, and pharmacists may be found on the manufacturer's websites: http://www.ultomirisrems.com.

Key References:

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3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
5. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006; 355(12):1233-1243.
6. Parker CJ, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005; 106(12):3699-3709.
7. Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011; 6:60.
8. Loirat C, Fakhouri F, Ariceta G, et al; HUS International. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2016; 31(1):15-39.
9. Sanders DB, Wolfe GI, Benatar M, et al for the Task Force of the Myasthenia Gravis Foundation of America (MGFA). International consensus guidance for management of myasthenia gravis. Neurology 2016; 87:419.
10. Narayanaswami P, Sanders DB, Wolfe G, et al for the Task Force of the Myasthenia Gravis Foundation of America (MGFA). International consensus guidance for management of myasthenia gravis 2020 update. Neurology 2021; 96:114-122.
11. Lee JW, Fontbrune FS, et al. Ravulizumab vs Eculizumab in Adult Patients with PNH Naïve to Complement Inhibitors: The 301 Study. Blood 2018; prepublished online December 3, 2018; DOI 10.1182/blood-2018-09-876136.
12. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2018; Pre-published online December 3, 2018; doi: 10.1182/blood-2018-09-876805.

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