OVERVIEW
Ultomiris is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) and for the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA). The safety and effectiveness of Ultomiris for the treatment of PNH in pediatric patients have not been established.

The recommended dosing regimen for adults with PNH consists of a weight-based loading dose (dosage range: 2,400 mg to 3,000 mg) followed by maintenance dosing (dosage range: 3,000 mg to 3,600 mg), administered by intravenous (IV) infusion. Starting 2 weeks after the loading dose administration, begin maintenance doses at a once every 8-week interval. The recommended dosing regimen for patients with aHUS consists of a weight-based loading dose (dosage range: 600 mg to 3,000 mg) followed by maintenance dosing (dosage range: 300 mg to 3,600 mg), administered by intravenous (IV) infusion. Starting 2 weeks after the loading dose administration, begin maintenance doses at a once every 4-week interval for patients ≥ 5 kg to < 20 kg or at a once every 8-week interval for patients ≥ 20 kg. For both PNH and aHUS the dosing schedule is allowed to occasionally vary within 7 days of the scheduled infusion day (with the exception of the first maintenance dose) but the subsequent dose should be administered according to the original schedule.

Disease Overview
PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias. Due to the absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations. GPI anchor protein deficiency is often due to mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in the first step of GPI anchor biosynthesis. Prior to the availability of Soliris® (eculizumab injection for IV) [a complement inhibitor], there was no specific therapy for PNH with only supportive management in terms of the cytopenias and control of thrombotic risk. Supportive measures used include platelet transfusion, immune suppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation. Soliris is the treatment of choice for patients with severe manifestations of PNH. Bone marrow transplantation is the only cure for PNH but should be reserved for patients with a suboptimal response to medication.

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy (TMA). The TMA process that characterizes HUS can be caused by a variety of things. Atypical HUS (aHUS) is a sub-type of HUS in which TMA are the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. Various aHUS-related mutations have been identified in genes of the complement system, which can explain approximately 60% of the aHUS cases, and a number of mutations and polymorphisms have been functionally characterized. aHUS should be distinguished from a more common condition referred to as typical HUS. The two disorders have different causes and different signs and symptoms. Unlike aHUS, the typical form is caused by infection with certain strains of Escherichia coli (E. coli) bacteria that produce toxic substances called Shiga-like toxins. The typical form is characterized
by severe diarrhea and most often affects children < 10 years of age, and it is less likely than aHUS to involve recurrent attacks of kidney damage that lead to end stage renal disease (ESRD). The incidence of aHUS is estimated to be 1:500,000 people/year in the US; aHUS is approximately 10 times less common than typical HUS.

Safety
Ultomiris has a Boxed Warning regarding life-threatening and fatal meningococcal infections. Meningococcal infections have occurred in patients receiving Ultomiris and may become rapidly life-threatening or fatal if not recognized and treated early. Ultomiris is contraindicated in patients with unresolved serious Neisseria meningitidis infection. Ultomiris has a Risk Evaluation and Mitigation Strategy (REMS) program to mitigate the occurrence and morbidity associated with meningococcal infections. The REMS program also educates healthcare professionals and patients regarding the increased risk of meningococcal infections with Ultomiris, the early signs of invasive meningococcal infections, and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections.

POLICY STATEMENT
Prior authorization is recommended for medical benefit coverage of Ultomiris. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Ultomiris as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Ultomiris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ultomiris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Paroxysmal Nocturnal Hemoglobinuria.** Approve Ultomiris for the duration noted if the patient meets ONE of the following (A or B):
   A) **Initial therapy.** Approve Ultomiris for 6 months if the patient meets the following criteria (i, ii, and iii):
      i. Patient is ≥ 18 years of age; AND
      ii. PNH diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND
      iii. Ultomiris is being prescribed by or in consultation with a hematologist; OR
   B) **Patient currently receiving Ultomiris.** Approve Ultomiris for 1 year if the patient is continuing to derive benefit (e.g., stabilization of hemoglobin levels, decreased transfusion requirements or
transfusion independence, reductions in hemolysis) from Ultomiris, according to the prescribing physician.

**Dosing.** Approve the dose if the patient meets the following weight-based regimen:
A) $\geq 40$ kg, the initial dose is $\leq 3,000$ mg administered by intravenous infusion for one dose, followed by $\leq 3,600$ mg administered by intravenous infusion not more frequently than once every 8 weeks.

2. **Atypical Hemolytic Uremic Syndrome.** Approve Ultomiris for 1 year if the patient meets the following criteria (A and B):
A) Patient does not have Shiga toxin *E. coli* related hemolytic uremic syndrome; AND
B) Ultomiris is being prescribed by or in consultation with a nephrologist.

**Dosing.** Approve the dose if the patient meets ONE of the following weight-based regimens (A or B):
A) $\geq 5$ kg to $< 20$ kg. The initial dose is $\leq 600$ mg administered by intravenous infusion for one dose, followed by $\leq 600$ mg administered by intravenous infusion not more frequently than once every 4 weeks; OR
B) $\geq 20$ kg. The initial dose is $\leq 3,000$ mg administered by intravenous infusion for one dose, followed by $\leq 3,600$ mg administered by intravenous infusion not more frequently than once every 8 weeks.

### CONDITIONS NOT RECOMMENDED FOR APPROVAL

1. Ultomiris has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

### REFERENCES
<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Date Reviewed</th>
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</thead>
<tbody>
<tr>
<td>New policy</td>
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<td>12/24/2018</td>
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<tr>
<td>Early annual revision</td>
<td>The condition of Atypical Hemolytic Uremic Syndrome, criteria, and dosing were added to the policy within the FDA-approved indications. The dosing for Paroxysmal Nocturnal Hemoglobinuria was changed from “One-time weight-based loading dose (≥ 40 kg to &lt; 60 kg: 2,400 mg; ≥ 60 kg to &lt; 100 kg: 2,700 mg; ≥ 100 kg: 3,000 mg). Followed by weight-based maintenance dosing of (≥ 40 kg to &lt; 60 kg: 3,000 mg; ≥ 60 kg to &lt; 100 kg: 3,300 mg; ≥ 100 kg: 3,600 mg). Starting 2 weeks after the loading dose administration, begin maintenance doses at a once every 8-week interval” to “≥ 40 kg, the initial dose is ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion not more frequently than once every 8 weeks.”</td>
<td>11/06/2019</td>
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