LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.571

C3 and C5 Complement Inhibitors

BCBSA Ref. Policy: 5.01.39

Effective Date:	Sept. 1, 2024	RELATED MEDICAL POLICIES:
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Replaces:	N/A	

Select a hyperlink below to be redirected to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
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Introduction

Empaveli (pegcetacoplan), Fabhalta (iptacopan), Soliris (eculizumab), and Ultomiris (ravulizumab-cwvz) are three drugs used to treat a rare blood condition called paroxysmal nocturnal hemoglobinuria (PNH). PNH can develop at any age. It most often appears when people are in their thirties and forties. It is a condition that develops from genetic changes (mutations) that happen during a person's lifetime. These genetic changes are not inherited, meaning they are not passed from parent to child. It is a life-threatening condition in which the immune system attacks and breaks down red blood cells. Soliris and Ultomiris can also be used to treat atypical hemolytic uremic syndrome (aHUS). In aHUS, blood clots form in the small blood vessels in the kidney. This condition usually arises from changes to certain genes in combination with other factors, such as the use of certain medications, chronic diseases, or infections. Most cases occur in people who do not have a family history of aHUS. In both PNH and aHUS, the genetic changes affect how the body makes certain proteins in the blood. These altered proteins can destroy red blood cells. Soliris and Ultomiris work by binding to these destructive proteins to prevent the breakdown of red blood cells. Soliris and Ultomiris are also approved for a third condition called generalized myasthenia gravis and Soliris has a fourth approved indication for the treatment of neuromyelitis optica spectrum disorder. An oral drug called Tavneos (avacopan) is approved for a condition which affects the small blood vessels in the body called anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. This inflammatory condition can result in damage to the kidneys and other organ systems. Syfovre

(pegcetacoplan) is an FDA approved drug to treat geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD). GA is caused by the gradual breakdown of light-sensitive cells in the macula that can lead to impaired vision or blindness. In the United States, approximately 1 million people have GA and most often appears when individuals are in their sixties. This policy describes when Empaveli, Fabhalta, Izervay, Soliris, Syfovre, Tavneos, Ultomiris, Veopoz, and Zilbrysq may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home.

Drugs subject to site of service review addressed in this policy are:

- Soliris (eculizumab) IV
- Ultomiris (ravulizumab-cwvz) IV

Click on the links below to be directed to the related medical necessity criteria:

Antineutrophil Cytoplasmic Autoantibody (ANCA)-Associated Vasculitis in Adults

Atypical Hemolytic Uremic Syndrome (aHUS) (Pediatric and Adult)

Generalized Myasthenia Gravis (gMG) in Adults

Geographic Atrophy (GA) Secondary to Dry Age-Related Macular Degeneration (AMD)

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* **Note:** *This does not include when standard dosing between infusions is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.** **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at**

Site of Service Administration	Medical Necessity
	increased risk of complications for infusions, including any ONE of the following: • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion therapy • A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.** **Note:** This policy does not address intravenous (IV) and injectable therapy services for individual's receiving inpatient services.

Condition	Medical Necessity
Paroxysmal Nocturnal Hemoglobinuria (PNH) • **Pediatric and Adult**	**Empaveli (pegcetacoplan) may be considered medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) when the following are met:** • The individual is aged 18 years or older **AND** • Has completed at least 3 months of therapy with *Soliris (eculizumab) or *Ultomiris (ravulizumab-cwvz) and has failed to achieve a hemoglobin level ≥ 10.5 g/dL **AND** • There is a documented diagnosis of PNH confirmed by granulocyte or monocyte clone size of ≥ 15% **AND**

Condition	Medical Necessity
	• Has received vaccinations against Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae at least 2 weeks prior to initiation of first dose **Note:** *Individuals are allowed short-term (4-weeks) of concomitant therapy when switching from Soliris or Ultomiris to reduce the risk of hemolysis with abrupt treatment discontinuation. Long-term concomitant therapy beyond 4-weeks with Soliris or Ultomiris is considered investigational. **Fabhalta (iptacopan) may be considered medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) when the following are met:** • The individual is aged 18 years or older **AND** • There is a documented diagnosis of PNH is confirmed by granulocyte or monocyte clone size of ≥ 15% **AND** • Has completed at least 3 months of therapy with *Soliris (eculizumab) or *Ultomiris (ravulizumab-cwvz) **AND** • Has experienced residual anemia defined as a hemoglobin < 10.5 g/dL AND lactic acid dehydrogenase (LDH) level 1.5 times the upper limit of normal while receiving treatment with *Soliris (eculizumab) or *Ultomiris (ravulizumab-cwvz) **AND** • Has received vaccinations against Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae at least 2 weeks prior to initiation of first dose **Note:** *Individuals are allowed short-term (4-weeks) of concomitant therapy when switching from Soliris or Ultomiris to reduce the risk of hemolysis with abrupt treatment discontinuation. Long-term concomitant therapy beyond 4-weeks with Soliris or Ultomiris is considered investigational. **Piasky (crovalimab-akkz) may be considered medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) when the following are met:**

Condition	Medical Necessity
	• The individual is aged 13 years or older **AND** • There is a documented diagnosis of PNH is confirmed by granulocyte or monocyte clone size of ≥ 15% **AND** • Has completed at least 3 months of therapy with *Soliris (eculizumab) or *Ultomiris (ravulizumab-cwvz) **AND** • Has experienced residual anemia defined as a hemoglobin < 10.5 g/dL AND lactic acid dehydrogenase (LDH) level 1.5 times the upper limit of normal while receiving treatment with *Soliris (eculizumab) or *Ultomiris (ravulizumab-cwvz) **AND** • Has received vaccinations against Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae at least 2 weeks prior to initiation of first dose **Note:** ***Individuals are allowed short-term (4-weeks) of concomitant therapy when switching from Soliris or Ultomiris to reduce the risk of hemolysis with abrupt treatment discontinuation. Long-term concomitant therapy beyond 4-weeks with Soliris or Ultomiris is considered investigational. **Soliris (eculizumab) may be considered medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) when the following are met:** • The individual is aged 18 years or older **AND** • There is a documented diagnosis of PNH confirmed with granulocyte or monocyte clone size of ≥ 15% **AND** • Treatment naïve individuals have active hemolysis as measured by lactic acid dehydrogenase (LDH) level of 1.5 times the upper limit of normal **AND** • Has received a vaccination against Neisseria meningitidis at least 2 weeks prior to initiation of first dose

Condition	Medical Necessity
	Ultomiris (ravulizumab-cwvz) IV may be considered medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) when the following are met: • The individual is aged one month of age or older **AND** • There is a documented diagnosis of PNH confirmed with granulocyte or monocyte clone size of ≥ 15% **AND** • Treatment naïve individuals have active hemolysis as measured by lactic acid dehydrogenase (LDH) level of 1.5 times the upper limit of normal **AND** • Received a vaccination against Neisseria meningitidis at least 2 weeks prior to initiation of first dose
Atypical Hemolytic Uremic Syndrome (aHUS) • **Pediatric and Adult**	**Soliris (eculizumab) may be considered medically necessary for the treatment of atypical hemolytic uremic syndrome (aHUS) when the following are met:** • There is documented microangiopathic hemolytic anemia established by a hemoglobin level < 8 g/dL with a negative Coomb's test and a peripheral blood smear demonstrating a large number of schistocytes (up to 10 percent of red cells) and helmet cells **AND** • There is documented thrombocytopenia with a platelet count less than 140,000/mm^3 **AND** • There is documented acute kidney injury established by renal function studies **AND** • The individual received a vaccination against Neisseria meningitidis at least 2 weeks prior to initiation of first dose **AND** • The individual does NOT have Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS)

Condition	Medical Necessity
	Ultomiris (ravulizumab-cwvz) IV may be considered medically necessary for the treatment of atypical hemolytic uremic syndrome (aHUS) when the following are met: • There is documented microangiopathic hemolytic anemia established by a hemoglobin level < 8 g/dL with a negative Coomb's test and a peripheral blood smear demonstrating a large number of schistocytes (up to 10 percent of red cells) and helmet cells **AND** • There is documented thrombocytopenia with a platelet count less than 140,000/mm^3 **AND** • There is documented acute kidney injury established by renal function studies **AND** • The individual received a vaccination against Neisseria meningitidis at least 2 weeks prior to initiation of first dose **AND** • The individual does NOT have Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS)
Generalized Myasthenia Gravis (gMG) • **Adult**	**Soliris (eculizumab) may be considered medically necessary in individuals with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive when the following are met:** • The individual is aged 18 years or older **AND** • There is a documented positive serologic test for anti-AchR antibodies **AND** • Is currently using the acetylcholinesterase inhibitor pyridostigmine, has tried and failed pyridostigmine or has contraindications to use of pyridostigmine **AND** • Is currently using two or more immunosuppressive therapies (ISTs) (e.g., glucocorticoids, azathioprine, mycophenolate mofetil, cyclosporine), has tried and failed two ISTs or has contraindications that prevent use of two ISTs

Condition	Medical Necessity
	AND • Has received a vaccination against Neisseria meningitidis at least 2 weeks prior to initiation of first dose **Ultomiris (ravulizumab-cwvz) IV may be considered medically necessary in adult individuals with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive when the following are met:** • The individual is aged 18 years or older **AND** • There is documented positive serologic test for anti-AchR antibodies **AND** • Is currently using the acetylcholinesterase inhibitor pyridostigmine, has tried and failed pyridostigmine or has contraindications to use of pyridostigmine **AND** • Is currently using two or more immunosuppressive therapies (ISTs) (e.g., glucocorticoids, azathioprine, mycophenolate mofetil, cyclosporine), has tried and failed two ISTs or has contraindications that prevent use of two ISTs **AND** • Has received a vaccination against Neisseria meningitidis at least 2 weeks prior to initiation of first dose **Zilbrysq (zilucoplan) SC may be considered medically necessary in adult individuals with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive when the following are met:** • The individual is aged 18 years or older (adult) **AND** • There is a documented positive serologic test for anti-AchR antibodies **AND** • Is currently using the acetylcholinesterase inhibitor pyridostigmine, has tried and failed pyridostigmine or has contraindications to use of pyridostigmine

Condition	Medical Necessity
	AND • Is currently using two or more immunosuppressive therapies (ISTs) (e.g., glucocorticoids, azathioprine, mycophenolate mofetil, cyclosporine), has tried and failed two ISTs or has contraindications that prevent use of two ISTs **AND** • Has received a vaccination against Neisseria meningitidis at least 2 weeks prior to initiation of first dose

Neuromyelitis optica spectrum disorder (NMOSD)
• **Adult**
	Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) may be considered medically necessary for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult individuals who are anti-aquaporin-4 (AQP4) antibody positive when the following are met:
	• The individual is aged 18 years or older (adult)
	AND
	• There is a documented diagnosis of NMOSD confirmed by:
	  ○ At least one of the following core clinical characteristics:
	  ▪ Optic neuritis
	  ▪ Acute myelitis
	  ▪ Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting
	  ▪ Acute brainstem syndrome
	  ▪ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
	  ▪ Symptomatic cerebral syndrome with NMOSD-typical brain lesions
	AND
	  ○ Positive test for AQP4-IgG antibodies
	AND
	  ○ Exclusion of alternative diagnoses (e.g., multiple sclerosis)
	AND
	• Has a history of at least 2 relapses in last 12 months or 3 relapses in the last 24 months
	AND
	• Has an Expanded Disability Status Scale (EDSS) score ≤ 7
	AND

Condition	Medical Necessity
	• Has received a vaccination against Neisseria meningitidis at least 2 weeks prior to initiation of first dose
Antineutrophil Cytoplasmic Autoantibody (ANCA)-Associated Vasculitis • **Adult**	**Tavneos (avacopan) may be considered medically necessary for the treatment of adult individuals with active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis when the following are met:** • The individual is aged 18 years or older **AND** • Has ANCA-associated vasculitis due to granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) **AND** • There is documentation of positive test for antibodies to PR3 (proteinase 3) or MPO (myeloperoxidase) **AND** • Tavneos is being used in combination with rituximab or cyclophosphamide
Geographic Atrophy (GA) Secondary to Dry Age-Related Macular Degeneration (AMD) • **Adult**	**Syfovre (pegcetacoplan) may be considered medically necessary for the treatment of individuals with geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) when the following are met:** • The individual is aged 60 years or older **AND** • There is documented diagnosis of geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) **AND** • Does not have GA secondary to other disease (e.g., Stargardt disease, cone rod dystrophy, or toxic maculopathies) **AND** • Does not have a diagnosis of choroidal neovascularization (CNV) in the same eye needing treatment **AND** • Has a normal luminance best corrected visual acuity (BCVA) of >24 letters (20/320 Snellen equivalent) **AND** • Total GA lesion size per eye is between 2.5 mm^2 to 17.5 mm^2 **AND**

Condition	Medical Necessity
	• Syfovre (pegcetacoplan) is not used concurrently with Izervay (avacincaptad pegol) **AND** • Is prescribed by or in consultation with an ophthalmologist **AND** • Dose prescribed is no greater than 15 mg every 25 days to each affected eye **Izervay (avacincaptad pegol) may be considered medically necessary for the treatment of individuals with geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) when the following are met:** • The individual is aged 50 years or older **AND** • There is a documented diagnosis of geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) **AND** • Does not have GA secondary to other disease (e.g., Stargardt disease, cone rod dystrophy, or toxic maculopathies) **AND** • Does not have a diagnosis of choroidal neovascularization (CNV) in the same eye needing treatment **AND** • Does not have a diagnosis of diabetic retinopathy in the same eye needing treatment **AND** • Izervay (avacincaptad pegol) is not used concurrently with Syfovre (pegcetacoplan) **AND** • Has a normal luminance best corrected visual acuity (BCVA) between 20/25 and 20/320 **AND** • Total GA lesion size per eye is between 2.5 mm^2 to 17.5 mm^2 **AND** • Prescribed by or in consultation with an ophthalmologist **AND**

Condition	Medical Necessity
	• Dose prescribed is no greater than 2 mg every 30 days to each affected eye **AND** • Total duration of therapy is ≤ 12 months
CD55-deficient protein-losing enteropathy(PLE) • **Pediatric and Adult**	**Veopoz (pozelimab-bbfg) may be considered medically necessary when:** • The individual is aged 1 year or older **AND** • Has a clinical diagnosis of CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease confirmed by biallelic CD55 loss-of-function mutation detected by genetic testing **AND** • The maximum prescribed maintenance dose is no more than 800 mg once weekly

Drug	Investigational
As listed	**All other uses of Empaveli (pegcetacoplan), Fabhalta (iptacopan), Izervay (avacincaptad pegol), Soliris (eculizumab), Syfovre (pegcetacoplan), Tavneos (avacopan), Ultomiris (ravulizumab-cwvz) IV, Veopoz (pozelimab-bbfg), and Zilbrysq (zilucoplan) is considered investigational.** **For Empaveli (pegcetacoplan) and Fabhalta (iptacopan) for the treatment of PNH, individuals are allowed short-term (4-weeks) of concomitant therapy when switching from Soliris or Ultomiris to reduce the risk of hemolysis with abrupt treatment discontinuation. Long-term concomitant therapy beyond 4-weeks with Soliris or Ultomiris is considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Empaveli (pegcetacoplan), Syfovre (pegcetacoplan), Soliris (eculizumab), Tavneos (avacopan), Ultomiris (ravulizumab-**

Length of Approval	
Approval	**Criteria**
	cwvz) IV, and Veopoz (pozelimab-bbfg) may be approved up to 6 months. **Izervay (avacincaptad pegol), Fabhalta (iptacopan), and Zilbrysq (zilucoplan) may be approved up to 12 months.**
Re-authorization criteria	**Future re-authorization of Empaveli (pegcetacoplan), Fabhalta (iptacopan), Soliris (eculizumab), Syfovre (pegcetacoplan), Tavneos (avacopan), Ultomiris (ravulizumab-cwvz) IV, Veopoz (pozelimab-bbfg), and Zilbrysq (zilucoplan) may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **Future re-authorization of Izervay (avacincaptad pegol) beyond 12 months is considered investigational.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, vaccination history and medication history

Coding

Code	Description
HCPCS	
C9162	Injection, avacincaptad pegol, (Izervay), 0.1 mg (code termed 4/1/2024)
J1300	Injection, eculizumab (Soliris), 10 mg
J1303	Injection, ravulizumab-cwvz, (Ultomiris) 10 mg
J1307	Injection, crovalimab-akkz, (Piasky) 10 mg (new code effective 1/1/2025)

Code	Description
J2781	Injection, pegcetacoplan, intravitreal, 1 mg
J2782	Injection, avacincaptad pegol (Izervay), 0.1 mg (new code effective 4/1/2024)
J3490	Unclassified drugs (Use to report Empaveli)
J9376	Injection, pozelimab-bbfg (Veopoz), 1 mg (new code effective 4/1/2024)

Related Information

Definition of Terms

Admitted: An individual who is receiving inpatient services with a doctor's order.

Hospital-based outpatient/outpatient services: These services include emergency department services, intravenous drug infusion or injection, observation services, outpatient surgery, lab tests, or X-rays, or any other hospital services, and the doctor hasn't written an order to admit the individual to a hospital as an inpatient. The individual's status is considered outpatient even if the individual spends the night in the hospital.

Infusion services: A service that provides infusion of a drug that is delivered directly into the bloodstream of an individual through a vein, usually located in the arm or hand.

Infusion center (aka, infusion suite): A location where an infusion service is provided and independent of a hospital.

Inpatient services: Services provided when an individual is formally admitted to the hospital with a doctor's order.

Consideration of Age

The age described in this policy for Site of Service reviews for medical necessity is 13 years of age or older. The age criterion is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right

venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatric unique physiology and psychology, site of service review is limited to individuals above the age of 13.

Ages stated in this policy for which the drugs are considered medically necessary are based on the FDA labeling for this drug.

Benefit Application

Medical Benefit

Soliris (eculizumab), Piasky (crovalimab-akkz) IV/SC, Ultomiris (ravulizumab-cwvz) IV, Veopoz (pozelimab-bbfg), Izervay (avacincaptad pegol), and Syfovre (pegcetacoplan) are managed through the medical benefit.

Pharmacy Benefit

Fabhalta (iptacopan), Tavneos (avacopan) and Zilbrysq (zilucoplan) are managed through the pharmacy benefit.

Medical / Pharmacy Benefit

Empaveli (pegcetacoplan) is managed through both the medical and pharmacy benefit.

Evidence Review

Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired genetic blood disorder characterized by hemolytic anemia, thrombosis, impaired bone marrow function and a 3% to 5% risk of developing leukemia. PNH typically affects people in young adulthood with a median age of 30-40 years. Soliris and Ultomiris are monoclonal antibodies that specifically binds to the

complement protein, thereby inhibiting generation of the terminal complement complex C5b-9. This mechanism of action allows Soliris and Ultomiris to inhibit terminal complement mediated intravascular hemolysis in PNH individuals. Empaveli is a C3 inhibitor which regulates the cleavage of the complement protein C3. C3 inhibition decreases opsonization of RBCs with C3 fragments as well as downstream complement activation, therefore, preventing intra- and extravascular hemolysis. C3 inhibitors differ from C5 inhibitors such as Soliris and Ultomiris which inhibit the complement protein C5 further down in the complement cascade and prevent intravascular hemolysis only. Previous treatment for PNH was dependent on the severity of individual symptoms, and the only curative therapy is allogenic bone marrow transplantation.

Atypical hemolytic uremic syndrome (aHUS) is a rare and chronic blood disease that can lead to kidney failure and is associated with increased risk of death and stroke. Safety and efficacy in pediatric individuals were found to be similar to adult individuals for the treatment of aHUS. Soliris and Ultomiris are a targeted therapy that works by inhibiting proteins that play a role in aHUS.

Myasthenia Gravis (MG) is an autoimmune disease that affects the neuromuscular junction and the characteristic finding of MG is muscle weakness that worsens with repeated use ("fatigable weakness"). The disease is progressive, and treatment typically includes high-dose corticosteroids combined with or followed by immunosuppressive drugs (most commonly azathioprine and mycophenolate mofetil). The goal of therapy is to maintain the individual with minimal manifestations of disease (no symptoms or functional limitations from MG despite minimal weakness on examination) or better. Currently, about 20,000 individuals with generalized MG are intolerant or have an inadequate response to conventional treatment options. The precise mechanism by which Soliris and Ultomiris provide therapeutic effect in gMG individuals is unknown but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

Vasculitis is the presence of inflammatory leukocytes in vessel walls resulting in damage. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a small vessel vasculitis includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). ANCA-associated vasculitis frequently presents with rapidly progressing glomerulonephritis and renal failure but can also affect other organ systems. The peak age of onset is between 65 and 74 years of age and is extremely rare in childhood. Data reporting prevalence and incidence of ANCA-associated vasculitis is lacking; however one study calculated the annual incidence in the US to be 3.3/100,000 and prevalence

to be 42/100,000. Mortality for ANCA-associated vasculitis is high, found to be twice as high in the first year as the back-ground rate for individuals of the same age and gender. Infective complications following treatment contribute significantly to morbidity and mortality. ANCA-associated vasculitis has a low incidence, and it is difficult to determine overall prevalence in the United States. It has been estimated to have 20 incident cases per million population per year in the UK, but this may be underestimated, and data is unavailable for the United States. The mechanism of ANCA-associated vasculitis is not well understood, but is associated with infectious, genetic, and environmental risk factors. These risk factors in addition to a "second hit" such as an infection or loss of gene silencing likely trigger development of autoantibodies that in turn activate neutrophils and the alternative complement pathway to cause microvascular injury and endothelial damage.

Geographic Atrophy (GA) is an advanced form of age-related macular degeneration (AMD) that can lead to progressive and irreversible vision loss. There are approximately one million people affected with GA in the United States. Syfovre (pegcetacoplan) is the first FDA approved treatment for GA secondary to AMD. Syfovre is a complement inhibitor that binds to components C3 and C3b to control excessive complement activation, which is associated with lesion growth in GA.

Summary of Evidence

Empaveli (pegcetacoplan)

Empaveli (pegcetacoplan) is a complement inhibitor indicated for the treatment of adult individuals with paroxysmal nocturnal hemoglobinuria (PNH). Empaveli has been studied for PNH in two Phase III trials, the completed PEGASUS trial, and the ongoing PRINCE trial and an open-label trial extension. Empaveli is also under study for cold agglutinin disease, hematopoietic stem cell transplant thrombotic microangiopathies, immune complex membranoproliferative glomerulonephritis, C3 glomerulopathy, and amyotrophic lateral sclerosis, although these potential indications have not been submitted to the FDA at this time.

The PEGASUS trial is a multicenter, randomized, open-label, 16-week, Phase 3 trial. Adult individuals with PNH who were uncontrolled on Soliris were eligible for inclusion. Individuals with <4 transfusions were limited to ≤50% of individuals enrolled. The trial included a 4-week run-in phase during which individuals received both Empaveli and Soliris, a 16-week randomization phase, and a 32-week, open-label Empaveli only phase. Individuals were randomized to Empaveli 1,080 mg twice weekly via SC infusion or to Soliris IV every two weeks. Randomization was stratified by the number of packed RBC transfusions in prior 12 months and

platelet count at screening. Transfusions were considered to confound results, and data was censored after the first transfusion. The primary endpoint was the change from baseline in Hb at week 16. Secondary endpoints during the randomized portion of the trial included transfusion avoidance, absolute reticulocyte count, lactate dehydrogenase (LDH) level, Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score at 16 weeks, and safety. The primary endpoint of the LS mean change in Hb at week 16 was significantly greater with Empaveli than Soliris (Hb +2.37 g/dL Empaveli, -1.47 g/dL Soliris, difference 3.84 g/dL, $p<0.0001$). This difference remained significant in individuals with <4 and ≥4 transfusions at baseline. At week 48 during the Empaveli only phase, Hb remained increased with Empaveli (+2.7 g/dL). Empaveli significantly increased transfusion avoidance compared to eculizumab (85.4% Empaveli vs 14.5% Soliris, $p<0.001$) and met criteria for noninferiority for LS mean difference in change from baseline in absolute reticulocyte count (-135.82 cells/L Empaveli vs 27.79 cells/L Soliris). However, change in LDH from baseline to week 16 did not meet criteria for noninferiority (-14.8 vs -10.1 U/L, respectively). Therefore, the change from baseline in FACIT-fatigue scores was not tested for significance; however, the difference was considered clinically significant (9.22 vs -2.65 Empaveli vs Soliris, difference 11.87). Overall, 73% of individuals on Empaveli were transfusion-free during the 48-week trial. During the 12 months before the study, 25% of individuals were transfusion-free while on eculizumab. Also, Hb normalization was achieved without transfusion in 34.1% of individuals on Empaveli compared to 0% on Soliris (difference 0.304, 95% CI 0.149-0.459).

The Prince trial is an ongoing, 26-week, multicenter, randomized, open-label, Phase III trial in adults with PNH who have not been treated with a complement inhibitor within 3 months. Individuals are randomized to Empaveli 1,080 mg SC twice weekly or standard of care (excluding complement inhibitors). The primary endpoints are Hb stabilization and reduction in LDH at week 26. Results are not yet available. A long-term extension trial is also ongoing, and no data is currently available. The extension is a multicenter, nonrandomized, open-label study in individuals with PNH who completed an Empaveli trial and experienced a clinical benefit. Enrollment of 160 individuals is planned and the primary endpoint is safety at 2 years.

Common adverse events (AEs) with Empaveli were infection (29%), diarrhea (22%), and injection-site erythema (17%). Altogether, injection-site reactions of all types (erythema, induration, swelling) occurred in 37% of individuals on Empaveli. Common AEs with Soliris were infection (26%), hemolysis (23%), and headache (23%). Of note, fatigue occurred in 15% of individuals on Soliris and 5% on Empaveli. The AE of hemolysis occurred in 10% of individuals on Empaveli compared to 23% on Soliris. However, three individuals (7%) on Empaveli discontinued treatment due to hemolysis compared to none with Soliris. The authors speculated a dosage adjustment may be necessary when starting Empaveli following Soliris.

Fabhalta (iptacopan)

The APPLY-PNH trial evaluated Fabhalta, administered twice daily, compared to anti-C5 therapies in adult individuals with PNH with residual anemia despite receiving a prior stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization. Individuals were randomized to receive Fabhalta monotherapy 200 mg twice daily or continue anti-C5 therapy for 24 weeks. Following completion of the 24-week randomized control period, all individuals were eligible to enroll in a 24-week treatment extension period and receive Fabhalta. Subsequently, individuals were eligible to enter a separate long-term extension (LTE) study. The APPOINT-PNH trial was a single-arm study in adults with PNH who were not previously treated with a complement inhibitor. This study enrolled a total of 40 adults with PNH (RBC clone size ≥10%), Hb <10 g/dL, and lactate dehydrogenase (LDH) levels >1.5 times the upper limit of normal (ULN). All 40 individuals received Fabhalta 200 mg orally twice daily during the 24-week open-label core treatment period. The APPLY-PNH trial met its co-primary endpoints: at 24 weeks, a higher proportion of individuals treated with Fabhalta achieved Hb increases of ≥2 g/dL from baseline without the need for blood transfusions, and a higher proportion of individuals achieved sustained Hb levels of ≥12 g/dL without the need for transfusions compared to individuals who continued to receive anti-C5 therapies. The most common adverse reactions for individuals in the APPLY-PNH trial included headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, nausea, and viral infection. Serious reactions occurred in 3% of individuals, including pyelonephritis, urinary tract infection, and COVID-19. In APPLY-PNH, serious adverse events were reported in two (3%) individuals with PNH receiving Fabhalta, which included pyelonephritis, urinary tract infection, and COVID-19. Common adverse events for individuals in the APPOINT-PNH study included headache, viral infection, nasopharyngitis, and rash. In APPOINT-PNH, serious adverse events were reported in two (5%) individuals with PNH receiving Fabhalta, which included COVID-19 and bacterial pneumonia. Three individuals had major adverse vascular events (MAVEs) during the APPLY-PNH trial: one individual in the randomized period and two individuals in the extension period.

Izervay (avacincaptad pegol)

Izervay (avacincaptad pegol) is a complement inhibitor indicated for the treatment of adult individuals with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Izervay is a pegylated oligonucleotide that binds to and inhibits complement protein C5

and as a result decreasing cleavage of C5a and C5b and membrane attack complex (MAC) formation. The use of Izervay is contraindicated in ocular or periocular infections and active intraocular inflammation.

The efficacy of Izervay for the treatment of AG secondary to AMD was established in GATHER 1, a phase 3 multicenter randomized, double-blind, placebo-controlled trial that enrolled 286 individuals with GA secondary to AMD. Individuals were treated with monthly injections of avacincaptad pegol or placebo for 18 months. A total of 176 individuals were randomized to receive Izervay and 110 were randomized to receive placebo. The primary endpoint of GATHER1 was change in GA area over 12 months. At 12 months, avacincaptad pegol showed less change in GA area than compared to placebo, the least square mean change in the square root was 0.292mm and 0.402mm for avacincaptad pegol 2mg and placebo respectively. The secondary endpoint was change in Best Corrected Visual Acuity (BCVA) and change in low luminance BCVA at 12 months. The change in BCVA was -7.9 and -9.3 for avacincaptad 2mg and placebo respectively. Avacincaptad pegol 2 mg or 4 mg did not have an impact on the mean change in BCVA or low luminance BCVA from baseline to month 12, compared with their corresponding placebo groups. Conjunctival hemorrhage, conjunctival hyperemia, punctuate keratitis and increased intraocular pressure (IOP) were the most frequently reported ocular adverse events (AEs) in GATHER1. There were no discontinuations across all treatment groups due to study drug.

The safety and efficacy of Izervay was established in the second phase 3 trial, GATHER 2, a multicenter, randomized, placebo-controlled trial. The primary endpoint was GA growth rate which was significantly less in the avacincaptad group compared to control, 1.75mm^2/year vs. 2.12mm^2/year respectively. In all clinical trials, avacincaptad was well-tolerated, however long-term safety data is still unknown. The safety and effectiveness of Izervay for the treatment of GA secondary to AMD in pediatric individuals under the age of 18 years have not been established. There is no safety data provided specific to GATHER2, the study publication is pending.

Soliris (eculizumab)

Soliris (eculizumab) is a complement inhibitor indicated for the treatment of individuals with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis, for the treatment of individuals age 18 and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy, for the treatment of adult individuals with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor antibody positive and for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult individuals who are anti-aquaporin-4 (AQP4) antibody positive. Soliris includes a boxed warning of life-

threatening and fatal meningococcal infections. Soliris is not indicated for the treatment of individuals with Shiga toxin E. coli- related hemolytic uremic syndrome (STEC-HUS). Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

The safety and effectiveness of Soliris for the treatment of PNH, gMG, and NMOSD in pediatric individuals under the age of 18 years have not been established. Four clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS included a total of 47 pediatric individuals (ages 2 months to 17 years). The safety and effectiveness of Soliris for the treatment of aHUS appear similar in pediatric and adult individuals.

The efficacy of Soliris for the treatment of neuromyelitis optica spectrum disorder (NMOSD) was established in NMOSD Study 1, a randomized, double-blind, placebo-controlled trial that enrolled 143 individuals with NMOSD who were anti-AQP4 antibody positive. A total of 96 individuals were randomized to receive Soliris treatment and 47 were randomized to receive placebo. During the treatment phase of the trial, 76% percent of individuals received concomitant immunosuppressive therapy (IST), including chronic corticosteroids; 24% of individuals did not receive concomitant IST or chronic corticosteroids during the treatment phase of the trial. The primary endpoint for NMOSD Study 1 was the time to the first adjudicated on-trial relapse. The time to the first adjudicated on-trial relapse was significantly longer in Soliris-treated individuals compared to placebo-treated individuals (relative risk reduction 94%; hazard ratio 0.058; $p < 0.0001$). Soliris-treated individuals experienced similar improvement in time to first adjudicated on-trial relapse with or without concomitant treatment. Soliris-treated individuals had a 96% relative reduction in the adjudicated on-trial annualized relapse rate (ARR) compared to individuals on placebo. Compared to placebo-treated individuals, Soliris-treated individuals had reduced annualized rates of hospitalizations (0.04 for Soliris versus 0.31 for placebo), of corticosteroid administrations to treat acute relapses (0.07 for Soliris versus 0.42 for placebo), and of plasma exchange treatments (0.02 for Soliris versus 0.19 for placebo).

Syfovre (pegcetacoplan)

Syfovre (pegcetacoplan) is a complement inhibitor indicated for the treatment of adult individuals with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Pegcetacoplan binds to complement protein C3, which in turn regulates the cleavage of C3 and the downstream effectors of complement activation.

Syfovre is administered 15 mg by intravitreal injection in each affected eye once every 25 to 60 days. Approval of Syfovre was based on results from two ongoing Phase 3 studies, DERBY (NCT03525600) and OAKS (NCT03525613). The results of the study DERBY and OAKS indicated that Syfovre reduced the rate of GA lesion growth through 24 months compared to sham by 18-22% in the OAKS trial, and 17-18% in the DERBY trial, based on the frequency of administration. Additionally, in the DERBY and OAKS clinical trials, Syfovre-treated individuals experienced a higher rate of new-onset exudative AMD (eAMD). At 24 months, 12% of individuals in the Syfovre monthly, 7% individuals in every other month group and 3% of individuals in the sham groups, developed eAMD.

The efficacy of Syfovre for the treatment of GA secondary to age related macular degeneration (AMD) was demonstrated in two randomized, double-masked, Sham-controlled, multicenter studies (DERBY and OAKS).

The DERBY study was phase 3, randomized, multi-center, double-masked and Sham-controlled study to compare the efficacy and safety of Syfovre compared to placebo in the individuals with geographic atrophy (GA) secondary to Age-related macular Degeneration (AMD). In this study, individuals were randomized in 2:2:1:1 ratio to one of these four groups: Syfovre administered 15 mg 0.1 ml monthly for 24 months (n = 201), Syfovre administered 15 mg 0.1 ml every other month for 24 months (n = 201), sham procedure administered monthly for 24 month or sham procedure administered every other month for 24 months (sham pooled n = 195). Syfovre was administered via intravitreal injection based on the randomization. The primary efficacy endpoint was a comparison of the change from baseline to month 12 between treatment groups in total area of GA lesions based on Fundus Autofluorescence (FAF). DERBY trial did not reach statistical significance difference between treatment groups at month 12. Compared to sham procedure group, the Syfovre reduced the GA lesion growth by 12% (p = 0.0609) in the monthly group compared to 11% (p = 0.0853) in every other month group.

The OAKS study was phase 3, randomized, multi-center, double-masked and Sham-controlled study to compare the efficacy and safety of Syfovre vs placebo in the individuals with geographic atrophy (GA) secondary to Age-related macular Degeneration (AMD). In this study, individuals were randomized in 2:2:1:1 ratio to one of these four groups: Syfovre administered 15 mg 0.1 ml monthly for 24 months (n = 202), Syfovre administered 15 mg 0.1 ml every other month for 24 months (n = 205) , sham procedure administered monthly for 24 month or sham procedure administered every other month for 24 months(sham pooled n = 207). Syfovre was administered via intravitreal injection based on the randomization. The primary efficacy endpoint was a comparison of the change in total area of GA lesions from baseline to month 12 between treatment groups. OAKS trial demonstrated statistically significant reduction in GA lesion growth compared to the sham procedure group at 12 months. Compared to sham

procedure group, the Syfovre reduced the GA lesion growth by 21% (p = 0.0004) in the monthly group compared to 16% (p = 0.0055) in every other month group.

The secondary efficacy endpoint was a comparison between treatment groups related to the incidence and severity of ocular and systemic adverse events in duration of 30 months. Most ocular adverse events were mild to moderate at month 12. Individuals experienced neovascular age-related macular degeneration, ocular discomfort, vitreous floaters, and conjunctival hemorrhage. Over 12 months, the infectious endophthalmitis rate was 0.047% per injection and intraocular inflammation rate was 0.22% per injection. Rate of Exudative AMD was 6.0% in the monthly group, 4.1% in every other month group and 2.4% in the sham group. The discontinuation rate in the DERBY study was 29% of the individuals in the monthly group, 22% of individuals in every other month group and 21% of the individuals in the sham procedure group. The discontinuation rate in OAKS study was 31% of the individuals in the monthly group, 21% of individuals in every other monthly group and 25% of the individuals in the sham procedure group.

Tavneos (avacopan)

Tavneos (avacopan) is a selective complement 5a receptor inhibitor for treatment of ANCA-associated vasculitis. This is a novel mechanism that blocks the C5a receptor in the pro-inflammatory complement system on blood neutrophils to prevent the cells from causing damage as a result of C5a activation, a known contributor to ANCA-associated vasculitis. Two phase II trials and one phase III trial have been conducted for the study of avacopan for ANCA-associated vasculitis. The CLEAR phase II study compared avacopan in combination with low-dose prednisone, avacopan alone, or prednisone plus placebo for noninferiority. The CLASSIC phase II study was primarily a safety study comparing avacopan 10 mg or 30 mg in addition to standard of care with standard of care alone.

The CLEAR study was a phase II, randomized, placebo-controlled, double-blind trial of avacopan in adults with newly diagnosed or relapsing vasculitis. 67 individuals were randomized to receive oral avacopan 30 mg twice daily plus reduced-dose prednisone (20 mg daily) (n=22), oral avacopan 30 mg twice daily without prednisone (n=22), or placebo plus prednisone starting at 60 mg daily (n=23). All individuals also received either cyclophosphamide or rituximab. Treatment response occurred in 86% and 81% of the avacopan with reduced-dose prednisone and avacopan with no prednisone groups, respectively, and in 70% in the high-dose glucocorticoid (control) group. Both avacopan groups met noninferiority criteria. Health Related Quality of Life (HRQoL) measured by the Short Form-36 (SF-36) and EuroQol-5 dimensions, 5 levels (EQ-5D-5L) indicated improvement with avacopan compared with control. Limitations

include the small sample size and lack of transparency around how many individuals in each group received cyclophosphamide compared to rituximab and thus it is unclear whether cyclophosphamide or rituximab may have influenced treatment response. It was mentioned that it was only a small number on rituximab because it had not yet been approved at the time of study.

The CLASSIC study was a phase II, randomized, placebo-controlled, double-blind trial of avacopan in adults with newly diagnosed (within 4 weeks) or relapsing vasculitis. 42 individuals were randomized to receive oral avacopan 10 mg twice daily plus standard of care (high-dose glucocorticoids plus cyclophosphamide or rituximab) (n=13), oral avacopan 30 mg twice daily with standard of care (n=16), or standard of care (n=13). This was primarily a safety study, with the primary endpoint of incidence of adverse events. Overall, AE rates appeared similar across all treatment arms. In the standard of care (SOC)-only treatment arm, 100% of individuals experienced at least one treatment-emergent AE, compared with 85% and 94% in the avacopan-10 and avacopan-30 treatment arms, respectively. Due to the small sample size and that this study was designed as a safety study, it was not powered for either safety or efficacy outcomes. It is difficult to draw conclusions about safety from this study because avacopan did not replace glucocorticoids in any arm, it was given in addition to standard of care.

The ADVOCATE study was a phase III, randomized, double-blind, double-dummy trial of avacopan in adults with newly diagnosed or relapsing granulomatosis with polyangiitis or microscopic polyangiitis for which treatment with cyclophosphamide or rituximab was indicated. 331 individuals were randomized to receive oral avacopan 30 mg twice daily plus prednisone-matched placebo (n=166) or oral prednisone taper plus avacopan-matched placebo (n=165). All individuals received either cyclophosphamide or rituximab. The primary endpoints were remission defined by Birmingham Vasculitis Activity Score (BVAS) score of 0 at week 26 and no glucocorticoid use in the previous 4 weeks and sustained remission defined as remission at both weeks 26 and 52. Avacopan was noninferior but not superior to prednisone taper for remission at week 26 and was superior to prednisone taper for sustained remission at week 52. Avacopan resulted in improvement in glucocorticoid-associated toxic effects, eGFR change from baseline, and HRQoL improvement from baseline to week 26 and 52 (SF-35 and EQ-5D-5L), but statistical significance was not reported. This study included both newly diagnosed and relapsing disease and was not powered to determine sub-group differences, so it may be difficult to determine if this therapy should be reserved for one group over another. Subgroup analyses comparing efficacy differences in individuals on cyclophosphamide versus rituximab were also not conclusive. Statistical significance was not reported for secondary end-points.

Ultomiris (ravulizumab-cwvz)

Ultomiris (ravulizumab-cwvz) is a complement inhibitor indicated for the treatment of adult and pediatric individuals one month of age and older with PNH, for the treatment of adult and pediatric individuals one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA), and for the treatment of adult individuals with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive. Ultomiris includes a boxed warning of life-threatening and fatal meningococcal infections. Ultomiris is available only through a restricted program under a REMS.

Ultomiris is a humanized monoclonal antibody complement component C5 that is virtually identify to Soliris but with a longer half-life. Soliris is given by IV infusion every two weeks while Ultomiris is given by IV infusion every eight weeks. Approval of Ultomiris for PNH was based on two open-label, randomized, active-controlled, non-inferiority phase 3 studies. The results of Study 301 and 302 demonstrated that Ultomiris was non-inferior to Soliris. Individuals did not receive a transfusion and had similar incidence of hemolysis measured by the normalization of LDH levels in individuals' blood.

The efficacy of Ultomiris for the treatment of gMG was demonstrated in a randomized, double-blind, placebo-controlled, multicenter study (ALXN1210-MG-306; NCT03920293). Individuals were randomized 1:1 to either receive Ultomiris (n=86) or placebo (n=89) for 26 weeks. Ultomiris was administered intravenously according to the weight-based recommended dosage.

Over 80% of individuals were receiving acetylcholinesterase inhibitors, 70% were receiving corticosteroids, and 68% were receiving non-steroidal immunosuppressants (ISTs) at study entry. Individuals on concomitant medications to treat gMG were permitted to continue on therapy throughout the course of the study.

The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the Myasthenia Gravis Activities of Daily Living profile (MG-ADL) total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. The total score ranges from 0 to 24, with the higher scores indicating more impairment. Treatment with Ultomiris demonstrated a statistically significant change in the MG-ADL and QMG total scores from baseline at Week 26 as compared to placebo.

Veopoz (pozelimab-bbfg)

CHAPLE disease is an ultra-rare and life-threatening genetic disorder of the immune system, which is activated by an overactivation of the complement system caused by CD55 gene mutation. CD55 gene mutation causes difficulty regulating the complement system. Overactive complement system tends to attack normal cell causing damages to the blood and lymph vessels along with the upper digestive tract and leading to loss of the circulating proteins.

Veopoz is a complement inhibitor indicated for the treatment of adult and pediatric individuals 1 year of age and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease. Veopoz is contraindicated in individuals with unresolved Neisseria meningitidis infection. It is recommended that individuals should be vaccinated or have a prophylaxis for meningococcal infection prior to first dose of Veopoz.

The safety and efficacy of Veopoz was evaluated in a single-arm study where the individuals' outcomes were compared with the pre-treatment data in individuals with active CD55- deficient protein-losing enteropathy (PLE) who had hypoalbuminemia. In this study, the individuals had to have a history of PLE and a confirmed genotype of biallelic CD55 loss of function mutation. In these individuals, active CD55-deficient PLE was defined as hypoalbuminemia (serum albumin level of $\leq$3.2 g/dL) with at least one of the following signs/symptoms in the previous six months: abdominal pain, diarrhea, peripheral edema, or facial edema. All the individuals received meningococcal vaccination prior to treatment with Veopoz and antibacterials for prophylaxis of meningococcal infection. All 10 individuals belonged to age group of 3 to 19 years of age with the mean baseline serum albumin concentration of 2.2 g/dL.

In this study, all individuals achieved normal level of serum albumin by week 12 and maintained serum albumin concentrations within the normal range through 72 weeks of treatment. The additional efficacy endpoint was the level of serum IgG concentrations. All individuals achieved normal range of serum IgG concentration within the first 12 weeks of the treatment and continued to maintain the normal range through 72 weeks of treatment.

The safety of Veopoz was studied in 10 individuals in the clinical trial. The most common adverse events were upper respiratory tract infection, fracture, urticaria and alopecia. Other adverse reactions include injection site reactions, metabolic acidosis, gingival.

Zilbrysq (zilucoplan)

Myasthenia gravis (MG) is the most common primary disorder of neuromuscular transmission and is characterized by weakness in ocular, bulbar, limb, and respiratory muscles. The degree of

muscle weakness can fluctuate and vary in severity from person to person; however, it will generally improve with rest and worsen with physical activity. Other precipitating factors include pregnancy, infection, surgery, and stress. Zilbrysq is a targeted C5 complement inhibitor for gMG that is administered subcutaneously once daily and that can be self-administered. Zilbrysq was evaluated in a Phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled study (RAISE; NCT04115293) in adult individuals with gMG who are anti-AChR antibody positive. At Week 12, treatment with Zilbrysq demonstrated a statistically significant improvement from baseline compared to placebo for MG-ADL total score and QMG total score. The proportion of MG-ADL responders with at least a 3-point improvement at Week 12 was greater for Zilbrysq (73.1%) compared to placebo (46.1%) ($P<0.001$). The proportion of QMG responders with at least a 5-point improvement was also greater for Zilbrysq (58%) compared to placebo (33%) ($P = 0.0012$). The proportion of clinical responders at higher response thresholds was consistently greater for Zilbrysq compared to placebo. The most common adverse reactions (≥10%) in individuals with gMG were injection site reactions, upper respiratory tract infection, and diarrhea. In RAISE, treatment-emergent adverse events (TEAEs) occurred in 66 individuals (77%) in the Zilbrysq group and in 62 individuals (70%) in the placebo group. The most common TEAE was injection site bruising (n = 14 [16%] in the Zilbrysq group and n = 8 [9%] in the placebo group). Incidences of serious TEAEs and serious infections were similar in both groups. One individual died in each group; neither death (COVID-19 [Zilbrysq] and cerebral hemorrhage [placebo]) was considered related to the study drug. Like other complement inhibitors for the treatment of gMG, Zilbrysq has a Black Box Warning related to serious meningococcal infections and is only available through a REMS program called the Zilbrysq REMS, in which prescribers must counsel individuals, provide information about the risk of meningococcal infections, and ensure that individuals are vaccinated with meningococcal vaccines.

Piasky (crovalimab-akkz)

Crovalimab-akkz has been studied in 3 phase III trials for the efficacy in adult individuals ≥ 18 years old with PNH. COMMODORE-2 and COMMODORE-3 were open-label studies that evaluated the efficacy of crovalimab-akkz in complement inhibitor naïve individuals, and were randomized and single-arm designs, respectively. COMMODORE-1 was a randomized, open-label, multicenter study that evaluated the efficacy of crovalimab-akkz in complement inhibitor experienced individuals. Across all three studies, crovalimab-akkz was demonstrated to have effective hemolysis control, transfusion avoidance, and hemoglobin stabilization. Crovalimab-akkz was demonstrated to be noninferior to eculizumab in COMMODORE-2 across the efficacy endpoints: hemolysis control, transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization. Individuals that switched from eculizumab to crovalimab-akkz maintained disease

control. Although a total of 5 pediatric patients were included in COMMODORE-1 and COMMODORE-3 the evidence is weak to determine the efficacy of crovalimab-akkz in the pediatric individuals at this time. There is a risk of transient immune complex reaction (Type III hypersensitivity) in patients who were complement inhibitor experienced and switching to crovalimab-akkz. The median time to onset was 1.6 weeks (0.7 – 4.4), and the median time to resolve was 1.9 weeks. Most reactions were mild to moderate and manifested as arthralgia and rash. There were no meningococcal infections across all three studies. Crovalimab-akkz's safety profile was comparable to that of eculizumab.

2019 Update

A literature search from January 1, 2018, through March 5, 2019, did not identify any new evidence that would change policy coverage for Soliris. On December 21, 2018, the FDA approved Ultomiris for the treatment of PNH.

2020 Update

Reviewed Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) prescribing information and conducted a literature search on the management of aHUS, gMG, NMOSD, and PNH. No new evidence found that would change this policy.

2021 Update

Reviewed Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) prescribing information. Updated Ultomiris criteria for the management of PNH to include pediatric individuals one month of age and older.

2022 Update

Reviewed prescribing information for all drugs in policy and conducted a literature search on the management of generalized myasthenia gravis (gMG). Added coverage for Ultomiris (ravulizumab-cwvz) for the treatment of adult individuals with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive.

2023 Update

Reviewed prescribing information for all drugs in policy and conducted a literature search on the management of geographic atrophy (GA). Added coverage for Syfovre (pegcetacoplan) for the treatment of adult individuals with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Added coverage for Veopoz (pozelimab-bbfg) for the treatment of adult and pediatric individuals 1 year of age and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease. Added coverage for Izervay (avacincaptad pegol) for the treatment of adult individuals with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Added coverage for Zilbrysq (zilucoplan) for the treatment of generalized myasthenia gravis (gMG) in adult individuals who are anti-acetylcholine receptor (AChR) antibody positive.

2024 Update

Reviewed prescribing information for all drugs in policy. Updated Ultomiris (ravulizumab-cwvz) to include coverage criteria for the treatment of certain individuals with neuromyelitis optica spectrum disorder (NMOSD). Added coverage criteria for Fabhalta (iptacopan) for the treatment of certain individuals with paroxysmal nocturnal hemoglobinuria (PNH). Updated the confirmed granulocyte clone size to ≥ 15% for Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Empaveli (pegcetacoplan) for the treatment of PNH. Removed Ultomiris (ravulizumab-cwvz) SC on-body injector coverage criteria as the product will not be available on the market. Added coverage criteria for Piasky (crovalimab-akkz) for the treatment of certain individuals with paroxysmal nocturnal hemoglobinuria (PNH).

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History

Date	Comments
03/01/17	New policy, approved February 14, 2017. Add to Prescription Drug section. This policy will be effective June 2, 2017, pursuant to provider 90-day notification.
07/01/17	Formatting update; added hyperlink menu for Medical Necessity sections.

Date	Comments
11/01/17	Interim Review, approved October 3, 2017. Clarified site of service exception criterion related to access: There is no outpatient infusion center within 50 miles of the patient's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.
02/14/18	Annual Review, approved February 6, 2018. Policy updated with literature review through January 2018. Approved February 13, 2018, to update hospital-based outpatient coverage from 30 days to 90 days.
03/01/18	Interim Review, approved February 27, 2018. Soliris criteria updated to include new FDA label indication.
09/21/18	Minor update. Added Consideration of Age statements.
11/01/18	Minor update, the Site of Service criteria was updated for clarity.
01/01/19	Minor update. Clarified Consideration of Age information.
04/01/19	Annual Review, approved March 12, 2019, effective July 4, 2019. Change policy title from" Soliris (eculizumab)" to "C5 Complement Inhibitors". Added drug Ultomiris (ravulizumab-cwvz) to policy. Added reference 6.
07/04/19	Coding update, added HCPCS code J3590.
09/01/19	Interim Review, approved August 13, 2019, effective December 5, 2019. Updated Soliris criteria and added indication for neuromyelitis optica spectrum disorder (NMOSD). Added HCPCS J1303 (new code effective 10/1/19), removed J3590.
02/01/20	Interim Review, approved January 23, 2020. Added Ultomiris for aHUS, same criteria as Soliris.
10/01/20	Annual Review, approved September 1, 2020. No changes to policy statements.
08/01/21	Annual Review, approved July 22, 2021. Updated Ultomiris (ravulizumab-cwvz) criteria for the management of PNH to include pediatric patients one month of age and older.
10/01/21	Interim Review, approved September 14, 2021. Changed policy title from C5 Complement Inhibitors to C3 and C5 Complement Inhibitors. Added Empaveli (pegcetacoplan) for the treatment of PNH in adults. Added HCPC codes J3490 & J3590, used to report Empaveli.
01/01/22	Interim Review, approved December 14, 2021. Added Tavneos (avacopan) for the treatment of adult patients with active ANCA-associated vasculitis.
07/01/22	Annual Review, approved June 14, 2022. Added coverage for Ultomiris (ravulizumab-cwvz) for the treatment of adult patients with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive.
01/01/23	Interim Review, approved December 13, 2022. For Empaveli (pegcetacoplan) revised bullet to require that the individual has completed at least 3 months of therapy with Soliris or Ultomoris and removed bullet on treatment naive individuals having active hemolysis as measured by LDH level of 1.5x the ULN due to policy requirement that the individual has tried Soliris or Ultomiris first. Added a note to Empaveli and updated

Date	Comments
	the investigational table regarding short-term concomitant therapy when switching from Soliris or Ultomiris and that long-term concomitant therapy with Soliris or Ultomiris is considered investigational. Added coverage for Ultomiris (ravulizumab-cwvz) SC on-body injector for the maintenance treatment of adults with PNH or aHUS. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/23	Annual Review, approved March 14, 2023. Added criteria for Syfovre (pegcetacoplan) for the treatment of individuals with geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD). Changed the wording from "patient" to "individual" throughout the policy for standardization. Syfovre added to HCPC codes J3490. Removed HCPC code J3590 and drug name Tavneos from HCPC code J3490.
07/01/23	Coding update. Added new HCPC code C9151.
10/01/23	Interim Review, approved September 12, 2023. Added coverage for Veopoz (pozelimab-bbfg) for the treatment of adult and pediatric individuals 1 year of age and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease. Added new HCPCS code J2781.
12/01/23	Interim Review, approved November 14, 2023. Added coverage for Izervay (avacincaptad pegol) for the treatment of geographic atrophy secondary to age-related macular degeneration (AMD). Added coverage for Zilbrysq (zilucoplan) for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Added Izervay to unspecified code J3490.
01/01/24	Coding update. Added new HCPCS code C9162.
04/01/24	Coding Update. Added new HCPCS codes J2782 and J9376. Termed HCPCS code C9162.
05/01/24	Annual Review, approved April 9, 2024. Updated Ultomiris (ravulizumab-cwvz) to include coverage criteria for the treatment of certain individuals with neuromyelitis optica spectrum disorder (NMOSD). Added coverage for Fabhalta (iptacopan) for the treatment of certain individuals with paroxysmal nocturnal hemoglobinuria (PNH). The following policy changes are effective August 2, 2024, following 90-day provider notification. Updated the confirmed granulocyte clone size to ≥ 15% for Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Empaveli (pegcetacoplan) for the treatment of PNH. HCPCS code C9151 termed 10/01/23.
09/01/24	Interim Review, approved August 13, 2024. Removed Ultomiris (ravulizumab-cwvz) SC on-body injector coverage criteria as the product will not be available on the market. Added coverage criteria for Piasky (crovalimab-akkz) for the treatment of certain individuals with paroxysmal nocturnal hemoglobinuria (PNH). Added HCPCS code J3590 for PiaSky.
01/01/25	Coding update. Added new HCPCS code J1307. Removed HCPCS Code J3590.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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呼籲提供免費的語言援助服務和適當的輔助設備及服務。
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Звертайтесь за безкоштовною мовною підтримкою та відповідними додатковими послугами.
សូមហៅទូរសព្ទទៅសេវាជំនួយភាសាដោយឥតគិតថ្លៃ ព្រមទាំងសេវាកម្ម និងជំនួយចាំបាច់ដែលសមរម្យផ្សេងៗ។
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Appelez pour obtenir des services gratuits d'assistance linguistique et des aides et services auxiliaires appropriés.
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