New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Empaveli™ (pegcetacoplan) [Apellis Pharmaceuticals, Inc.]**
Dosage Formulations:	1,080 mg/20 mL (54 mg/mL) single dose vial
FDA Approval Date: **FDB File Date:**	FDA: May 14, 2021 FDB: May 23, 2021
Indication:	Empaveli is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).
Mechanism of Action:	Empaveli binds to complement protein C3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, extravascular hemolysis (EVH) is facilitated by C3b opsonization while intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Empaveli acts proximally in the complement cascade controlling both C3b-mediated EVH and terminal complement-mediated IVH
Dose/ Administration:	Recommended dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump. • Dosage for patients switching to Empaveli from C5 inhibitors: To reduce the risk of hemolysis with abrupt treatment discontinuation: ○ For patients switching from Soliris® (eculizumab), initiate Empaveli while continuing Soliris at its current dose. After 4 weeks, discontinue Soliris before continuing on monotherapy with Empaveli. ○ For patients switching from Ultomiris® (ravulizumab-cwvz), initiate Empaveli no more than 4 weeks after the last dose of Ultomiris. • Dose adjustment: ○ For lactate dehydrogenase (LDH) levels greater than 2 times the upper limit of normal (ULN), adjust the dosing regimen to 1,080 mg every three days. ○ In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks. • Missed dose: ○ Administer Empaveli as soon as possible after a missed dose. Resume the regular dosing schedule following administration of the missed dose. • Empaveli is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous infusion, a patient may self-administer, or the patient's caregiver may administer Empaveli, if a healthcare provider determines that it is appropriate. • Prior to use, allow Empaveli to reach room temperature for approximately 30 minutes. Keep vial in carton until ready to use to protect from light. • Rotate infusion sites (i.e., abdomen, thighs, hips, upper arms) from one infusion to the next. If multi-infusion sets are needed, ensure the infusion sites are at least 3 inches apart. • The typical infusion time is approximately 30 minutes (if using two infusion sites) or approximately 60 minutes (if using one infusion site).
Disease State Clinical Highlights:	• PNH is a rare acquired disorder in which hematopoietic stem cells and their cellular progeny have lost the ability to anchor certain proteins to the cell surface. It may develop on its own (primary PNH) or in the context of other bone marrow disorders such as aplastic anemia (secondary PNH). • The estimated incidence of PNH is in the range of 1 to 10 cases per million population, equating to 5,000-6,000 patients in the U.S. It is a disease of mostly adults, although it has been reported in children. The median age of onset is in the 30's, and it lasts lifelong.

	• The body's immune system, the complement system, causes destruction of red blood cells. The destruction occurs due to the presence of defective surface protein, DAF, on the red blood cell, which normally functions to inhibit such immune reactions. The complement cascade attacks the red blood cells within the blood vessels of the circulatory system and causes hemolysis.
	• PNH is categorized based on the presence of symptoms and findings from bone marrow examination. It is a dynamic condition and the category of PNH may evolve over time. The three categories of PNH are: hemolytic (classical) PNH, subclinical PNH, and PNH with bone marrow failure.
	• PNH is the only hemolytic anemia caused by an acquired (rather than inherited) intrinsic defect in the cell membrane (deficiency of glycophosphatidylinositol leading to the absence of protective proteins on the membrane). Loss of the complement inhibitors, CD55 and CD59, on the surface of red blood cells (RBC) leads to chronic and/or paroxysmal intravascular hemolysis and a propensity for thrombosis.
	• Clinical Findings, Signs and Symptoms:
	  ○ Hemolytic anemia-characterized by fatigue, jaundice, and red/pink/black urine
	  ○ Fatigue
	  ○ Dyspnea
	  ○ Hemoglobinuria
	  ○ Abdominal pain
	  ○ Bone marrow suppression-may lead to other cytopenias
	  ○ Erectile dysfunction
	  ○ Chest pain
	  ○ Thrombosis in an atypical location (e.g., abdominal or cerebral vein)
	  ○ Hypercoagulable state induced by complement activation
	  ○ Free hemoglobin (Hb) in the blood stream
	  ○ Renal insufficiency
	  ○ Pulmonary hypertension
	• Expert panel recommendations from the American Society of Hematology advise that for patients with symptomatic hemolytic PNH (including those with thrombosis, organ dysfunction, or pain) who do not have severe bone marrow failure (BMF), treatment should include a complement inhibitor, rather than supportive care alone or allogeneic bone marrow transplant. Compared with transplantation or supportive care alone, complement inhibitors offer a more favorable profile of toxicity and efficacy for hemolytic PNH.
	• The primary goal of treatment with a complement inhibitor is alleviation of PNH-related symptoms (e.g. fatigue, dyspnea), elimination of transfusion-dependence, prevention of thromboses, and relief of pain. Complement inhibitors do not mitigate symptoms and complications of PNH-associated BMF, such as aplastic anemia or myelodysplastic syndrome.

Drug Clinical Highlights:	• Although Empaveli is not the first medication approved to treat PNH, it is the only C3 complement inhibitor currently on the market. Since it works earlier in the complement cascade process, it can inhibit both intravascular and extravascular hemolysis. Since C5 inhibitors only affect intravascular hemolysis, Empaveli may reduce the number of transfusions PNH patients need as compared to being treated with Soliris or Ultomiris. The data from the PEGASUS study show noninferiority to Soliris in transfusion avoidance.
	• Empaveli is contraindicated in:
	  ○ Patients with hypersensitivity to any component of the formulation
	  ○ Patients who are not currently vaccinated against certain encapsulated bacteria unless the risks of delaying Empaveli treatment outweigh the risk of developing a serious bacterial infection with an encapsulated organism.
	  ○ Patients with unresolved serious infection caused by encapsulated bacteria (i.e., *S. pneumoniae, N. meningitidis, and H. influenzae*).
	• **<u>Black Box Warning</u>: Serious Infections Caused by Encapsulated Bacteria-Meningococcal infections may occur in patients treated with Empaveli and may**

become rapidly life-threatening or fatal if not recognized and treated early. Use of Empaveli may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *S. pneumoniae, N. meningitidis* types A, C, W, Y and B, and *H. influenzae* type B.
    - **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients with altered immunocompetence associated with complement deficiencies.**
    - **Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of Empaveli unless the risks of delaying therapy with Empaveli outweigh the risk of developing serious infection.**
    - **Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.**
    - **Empaveli is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Empaveli REMS, prescribers must enroll in the program.**
- Additional Warnings and Precautions:
    - Infusion-related reactions- Systemic hypersensitivity reactions (e.g., facial swelling, rash, and urticaria) have occurred in patients treated with Empaveli.
    - Monitoring PNH manifestations after discontinuation of Empaveli- Closely monitor for signs and symptoms of hemolysis, identified by elevated LDH levels along with sudden decrease in PNH clone size or hemoglobin, or reappearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues Empaveli for at least 8 weeks to detect hemolysis and other reactions. If hemolysis, including elevated LDH, occurs after discontinuation of Empaveli, consider restarting treatment with Empaveli.
    - Interference with laboratory tests- There may be interference between silica reagents in coagulation panels and Empaveli that results in artificially prolonged activated partial thromboplastin time (aPTT); therefore, avoid the use of silica reagents in coagulation panels.

Clinical Trial-PEGASUS (NCT03500549)
- The efficacy and safety of Empaveli in patients with PNH was assessed in a multicenter, randomized, open-label, active comparator-controlled, 16-week Phase 3 study.
- Study population:
    - Patients with PNH
    - Patients had been treated with a stable dose of Soliris for at least the previous 3 months
    - With hemoglobin (Hb) levels less than 10.5 g/dL
    - Patients were vaccinated against *S. pneumoniae, N. meningitidis* types A, C, W, Y and B, and *H. influenzae* type B within 2 years prior to Day 1 or within 2 weeks after starting treatment with Empaveli. Those vaccinated after initiating treatment with Empaveli, received prophylactic antibiotic therapy until 2 weeks after vaccination.
- Eligible patients entered a 4-week run-in period during which they received Empaveli 1,080 mg subcutaneously twice weekly in addition to their current dose of Soliris.
- Treatment Regimen:
    - Patients (N=80) were then randomized in a 1:1 ratio to receive either 1,080 mg of Empaveli twice weekly or their current dose of Soliris through the duration of the 16-week randomized controlled period (RCP).
    - If required, the dose of Empaveli could be adjusted to 1,080 mg every 3 days. Empaveli was administered as a subcutaneous infusion; the infusion time was approximately 20 to 40 minutes.

- Following completion of the RCP, all patients entered a 32-week open-label period and received monotherapy with Empaveli.

- The efficacy of Empaveli was based on change from baseline to Week 16 (during the RCP) in Hb level. Supportive efficacy data included transfusion avoidance and change in absolute reticulocyte count (ARC) from baseline to Week 16.

	Empaveli (N=41)	**Soliris** (N=39)	**Difference** (95% CI)
Primary Efficacy Data			
Change in Hb level from baseline at Week 16	2.37 g/dL	-1.47 g/dL	3.84 g/dL (2.33, 5.34) [p<0.0001]
Secondary Efficacy Data			
Transfusion Avoidance, n (%)	35 (85%)	6 (15%)	63%* (48%, 77%)
Change from baseline in ARC (10^9 cells/L), LS** mean (SE)***	-136 (6.5)	28 (11.9)	-164 (-189.9, 137.3)

* Difference in percentages and 95% CI were based on the stratified Miettinen-Nurminen method
**LS = Least square
***SE = Standard error

- Empaveli was superior to Soliris for the change from baseline in Hb level at Week 16 (p<0.0001).
- Non-inferiority was demonstrated in the endpoint of transfusion avoidance and change from baseline in ARC. Noninferiority was not shown for the change from baseline in LDH levels.

Price Per Unit (WAC):

$458,000 per year.

Therapeutic Alternatives:

Empaveli is the first C3 complement inhibitor approved to treat PNH although other C5 complement inhibitor therapies have been on the market since 2007 (Soliris) and 2018 (Ultomiris). Medications for PNH are not curative but do alleviate symptoms and increase quality of life. Allogeneic bone marrow transplant is the only cure; however, it is limited by significant morbidity and mortality. Ultomiris is a humanized monoclonal antibody engineered from Soliris. It is clinically noninferior to Soliris but with a longer half-life. Approximately one-third of patients treated with Soliris and Ultomiris still require blood transfusions.

	Soliris® (eculizumab)	**Ultomiris®** (ravulizumab-cwvz)	**Empaveli™** (pegcetacoplan)
Manufacturer	Alexion	Alexion	Apellis
Year Approved by FDA	2007	2018	2021
Mechanism of Action	C5 complement inhibitor	C5 complement inhibitor	C3 complement inhibitor
Route of Administration	IV infusion	IV infusion	Subcutaneous infusion
Age Indication for PNH	≥18 years of age	≥1 month of age	≥18 years of age
Dose	600 mg every 7 days for first 4 weeks, then 900 mg 7 days after the 4th dose, then 900 mg every 14 days	Weight based loading and maintenance dose, given every 8 weeks 70kg patient: 2,700 mg loading dose then 3,300 mg maintenance dose	1,080 mg twice weekly

Availability	Soliris REMS	Ultomiris REMS	Empaveli REMS
Boxed Warnings	Fatal meningococcal infections	Life-threatening meningococcal infections	Life-threatening or fatal meningococcal infections
Other indications	• aHUS to inhibit complement-mediated thrombotic microangiopathy • Anti-acetylcholine antibody positive generalized myasthenia gravis • Anti-AQP4 antibody positive NMOSD	• aHUS to inhibit complement-mediated thrombotic microangiopathy	None
Cost (WAC)/Year	$508,786 (maintenance dose)	$493,115 (maintenance dose)	$458,000
LOE	Upon approval	March 6, 2035 or October 26, 2038	2035

Abbreviations: aHUS = atypical hemolytic uremic syndrome; AQP4 = Aquaporin-4; NMOSD = neuromyelitits optica spectrum disorder; REMS = Risk Evaluation and Mitigation Strategy

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with a hematologist, oncologist, or immunology specialist or other expert in the disease state **AND**
- Age ≥ 18 years **AND**
- Must have a laboratory-confirmed diagnosis of PNH (flow cytometry, LDH level of 1.5 times the upper limit of normal, bone marrow aspirate and biopsy) **AND**
- Must have documented full-course of meningococcal, pneumococcal, and Hib vaccines or a test for antibodies against encapsulated bacteria at least 2 weeks before starting treatment (unless benefits outweigh the risks to starting therapy) **AND**
- Patient is transfusion-dependent (Hb ≤ 7 g/dL or Hb ≤ 9 g/dL and member is experiencing symptoms of anemia) **OR**
- Has symptoms of thromboembolic complications (abdominal pain, shortness of breath, chest pain, end-organ damage)
- Approval period: 6 months

Continuation of Therapy:

- Patient has experienced an improvement or less than expected decline in fatigue and quality of life, a decrease in transfusions, increase in Hb levels, or normalization of LDH levels.
- Booster dose of MenACWY vaccine every 5 years, for the duration of complement inhibitor therapy (CDC recommendation)
- Booster dose of MenB vaccine 1 year after series completion and then every 2 to 3 years thereafter for the duration of complement inhibitor therapy (CDC recommendation)
- Approval period: 1 year

Additional Provider Diagnostic/Monitoring Criteria, if desired:

- Documentation demonstrating a positive clinical response from baseline, which includes an increase in or stabilization of Hb levels, a reduction in transfusions, or normalization in LDH levels

Implication to State Medicaid Program:	**LOE: 14 years after FDA approval**
	• The data from a clinical trial (PRINCE) in complement inhibitor treatment-naïve patients are expected to be available in 2Q 2021, which will help determine Empaveli's role as a first-line therapy for PNH.
	• Empaveli is also being evaluated in the following complement-mediated diseases:
	  ○ Complement 3 glomerulopathy
	  ○ Geographic atrophy
	  ○ Amyotrophic lateral sclerosis
	• Alexion is expected to file for approval of a once-weekly Ultomiris SC injection in 3Q 2021.
	• In December 2020, AstraZeneca announced that it had reached an agreement to acquire Alexion.
	• Crovalimab (R07112689) from Chugai, is a complement inhibitor given IV or SC is in Phase 3 trials with an expected completion date of October 2024.
	• Danicopan (ALXN2040) from Alexion, is an oral factor D inhibitor in Phase 3 trials for add-on therapy for PNH patients with EVH with an estimated study completion in December 2023.
	• Iptacopan (LNP023) from Novartis, is an oral, highly selective factor B inhibitor of the alternative complement pathway granted breakthrough therapy designation by the FDA for the treatment of PNH based on positive interim results of two ongoing Phase 2 studies.
	• The Loss of Exclusivity for Soliris is expected in 2025 and Amgen has a biosimilar version in Phase 1 studies that may launch 1H 2023.
	• ACH4471 from Achillion Pharmaceuticals, is a factor D inhibitor that blocks PNH cell hemolysis, mitigates the accumulation of C3 fragments on the surface of PNH cells, and also blocks the APC in in vitro models of aHUS. It has been granted orphan drug designation for the treatment of PNH in the U.S.
	• C1 Esterase Inhibitors (Berinert, Cinryze, and Haegarda) are used to treat C1 esterase deficiency in hereditary or acquired angioedema. C1 esterase inhibitors prevent the early stages of complement activation and associated inflammatory proteases, possibly able to play a role in blocking the accumulation of C3 degradation products on CD55-deficient erythrocytes in earlier phases of the complement cascade than that currently inhibited by Soliris for incomplete responders or non-responders to that therapy.

References:

1. Empaveli (pegcetacoplan) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2021.
2. IPD Analytics. *Hematologic: Paroxysmal Nocturnal Hemoglobinuria (PNH) Therapy*. https://secure.ipdanalytics.com. Accessed May 21, 2021.
3. Brodsky, Robert A., MD. *Treatment and Prognosis of Paroxysmal Nocturnal Hemoglobinuria*. UpToDate. https://www.uptodate.com/contents/treatment-and-prognosis-of-paroxysmal-nocturnal-hemoglobinuria. Accessed May 25, 2021.
4. Centers for Disease Control and Prevention. *Managing the Risk of Meningococcal Disease among Patients Who Receive Complement Inhibitor Therapy*. https://www.cdc.gov/meningococcal/clinical/eculizumab.html. Accessed June 4, 2021.