

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EMPAVELI safely and effectively. See full prescribing information for EMPAVELI.

EMPAVELI® (pegcetacoplan) injection, for subcutaneous use  
Initial U.S. Approval: 2021

### WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

See full prescribing information for complete boxed warning.

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 *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B. (5.1)

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria. (5.1)
- Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of EMPAVELI unless the risks of delaying EMPAVELI therapy outweigh the risks of developing a serious infection. See *Warnings and Precautions* (5.1) for additional guidance on managing the risk of serious infections.
- 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. (5.1)

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. (5.2)

### INDICATIONS AND USAGE

EMPAVELI is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). (1)

### DOSAGE AND ADMINISTRATION

- Recommended dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available pump. (2.2)

- See Full Prescribing Information for instructions on preparation and administration. (2.2, 2.3)

### DOSAGE FORMS AND STRENGTHS

- Injection: 1,080 mg/20 mL (54 mg/mL) in a single-dose vial. (3)

### CONTRAINDICATIONS

EMPAVELI is contraindicated in:

- Patients with hypersensitivity to pegcetacoplan or any of the excipients. (4)
- Patients who are not currently vaccinated against certain encapsulated bacteria unless the risks of delaying EMPAVELI treatment outweigh the risks of developing a serious bacterial infection with an encapsulated organism. (4, 5.1)
- Patients with unresolved serious infection caused by encapsulated bacteria. (4)

### WARNINGS AND PRECAUTIONS

Use caution when administering EMPAVELI to patients with:

- Serious infections caused by encapsulated bacteria. (5.1)
- Infusion-Related Reactions: Monitor patients for infusion-related reactions and institute appropriate medical management as needed. (5.3)
- Interference with Laboratory Tests: Use of silica reagents in coagulation panels may result in artificially prolonged activated partial thromboplastin time (aPTT). (5.5)

### ADVERSE REACTIONS

Most common adverse reactions in patients with PNH (incidence  $\geq 10\%$ ) were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, pain in extremity, hypokalemia, fatigue, viral infection, cough, arthralgia, dizziness, headache, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apellis Pharmaceuticals, Inc. at 1-833-866-3346 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2023

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## FULL PRESCRIBING INFORMATION

### WARNING: 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 *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B [see *Warnings and Precautions* (5.1)].

- 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 a serious infection. See *Warnings and Precautions* (5.1) for additional guidance on the management of the risk of serious infections.
- 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 [see *Warnings and Precautions* (5.2)]. Enrollment in the EMPAVELI REMS program and additional information are available by telephone: 1-888-343-7073 or at [www.empavelirems.com](http://www.empavelirems.com).

## 1 INDICATIONS AND USAGE

EMPAVELI® is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Vaccination and Prophylaxis

Vaccinate patients against encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B at least 2 weeks prior to initiation of EMPAVELI therapy according to current ACIP guidelines [see *Warnings and Precautions* (5.1)].

Provide 2 weeks of antibacterial drug prophylaxis to patients if EMPAVELI must be initiated immediately and vaccines are administered less than 2 weeks before starting therapy with EMPAVELI.

Healthcare professionals who prescribe EMPAVELI must enroll in the REMS for EMPAVELI [see *Warnings and Precautions* (5.2)].

### 2.2 Dosage

The recommended dose of EMPAVELI is 1,080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump with a reservoir of at least 20 mL.

#### Dosage for patients switching to EMPAVELI from C5 inhibitors

To reduce the risk of hemolysis with abrupt treatment discontinuation:

- For patients switching from eculizumab, initiate EMPAVELI while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with EMPAVELI.
- For patients switching from ravulizumab, initiate EMPAVELI no more than 4 weeks after the last dose of ravulizumab.

#### Dose Adjustment

- For lactate dehydrogenase (LDH) levels greater than 2 × 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.

### **2.3 Administration**

**EMPAVELI is for subcutaneous infusion using an infusion pump.**

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.

- Refer to the EMPAVELI Instructions for Use and the infusion pump manufacturer's instructions for full preparation and administration information.
- Use aseptic technique when preparing and administering EMPAVELI.
- Prior to use, allow EMPAVELI to reach room temperature for approximately 30 minutes. Keep the vial in the carton until ready for use to protect from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. EMPAVELI is a clear, colorless to slightly yellowish solution. Do not use if the liquid looks cloudy, contains particles, or is dark yellow.
- Use a needleless transfer device (such as a vial adapter) or a transfer needle to fill the syringe.
- Rotate infusion sites (i.e., abdomen, thighs, hips, upper arms) from one infusion to the next. Do not infuse where the skin is tender, bruised, red, or hard. Avoid infusing into tattoos, scars, or stretch marks.
- 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).
- Discard any unused portion.

### **3 DOSAGE FORMS AND STRENGTHS**

Injection: 1,080 mg/20 mL (54 mg/mL) clear, colorless to slightly yellowish solution in a single-dose vial.

### **4 CONTRAINDICATIONS**

EMPAVELI is contraindicated in:

- Patients with hypersensitivity to pegcetacoplan or to any of the excipients.
- Patients who are not currently vaccinated against certain encapsulated bacteria, unless the risks of delaying EMPAVELI treatment outweigh the risks of developing a bacterial infection with an encapsulated organism [see *Warnings and Precautions (5.1)*].
- Patients with unresolved serious infection caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Serious Infections Caused by Encapsulated Bacteria**

The use of EMPAVELI may predispose individuals to serious, life-threatening, or fatal infections caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B (Hib). To reduce the risk of infection, all patients must be vaccinated against these bacteria according to the most current ACIP recommendations for patients with altered immunocompetence associated with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with EMPAVELI.

For patients without known history of vaccination, administer required vaccines at least 2 weeks prior to receiving the first dose of EMPAVELI. If immediate therapy with EMPAVELI is indicated, administer required vaccine as soon as possible and provide patients with 2 weeks of antibacterial drug prophylaxis.

Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider discontinuation of EMPAVELI in patients who are undergoing treatment for serious infections.

## **5.2 EMPAVELI REMS**

Because of the risk of serious infections, EMPAVELI is available only through a restricted program under a REMS. Under the EMPAVELI REMS, prescribers must enroll in the program.

Prescribers must counsel patients about the risk of serious infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated against encapsulated bacteria.

Enrollment in the EMPAVELI REMS and additional information are available by telephone: 1-888-343-7073 or at [www.empavelirems.com](http://www.empavelirems.com).

## **5.3 Infusion-Related Reactions**

Systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria) have occurred in patients treated with EMPAVELI. One patient (less than 1% in clinical studies) experienced a serious allergic reaction which resolved after treatment with antihistamines. If a severe hypersensitivity reaction (including anaphylaxis) occurs, discontinue EMPAVELI infusion immediately, institute appropriate treatment, per standard of care, and monitor until signs and symptoms are resolved.

## **5.4 Monitoring PNH Manifestations after Discontinuation of EMPAVELI**

After discontinuing treatment with 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.

## **5.5 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.

# **6 ADVERSE REACTIONS**

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Infections Caused by Encapsulated Bacteria [*see Warnings and Precautions (5.1)*]
- Infusion-Related Reactions [*see Warnings and Precautions (5.3)*]

## **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

## Paroxysmal Nocturnal Hemoglobinuria

### Study in Complement-Inhibitor Experienced Adult Patients with PNH (Study APL2-302)

The data described below reflect the exposure in 80 adult patients with PNH who received EMPAVELI (n=41) or eculizumab (n=39) at the recommended dosing regimens for 16 weeks. Serious adverse reactions were reported in 7 (17%) patients with PNH receiving EMPAVELI. The most common serious adverse reaction in patients treated with EMPAVELI was infections (5%). The most common adverse reactions ( $\geq 10\%$ ) with EMPAVELI were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue.

Table 1 describes the adverse reactions that occurred in  $\geq 5\%$  of patients treated with EMPAVELI in Study APL2-302.

**Table 1: Adverse Reactions Reported in  $\geq 5\%$  of Patients Treated with EMPAVELI in Study APL2-302**

Adverse Reaction	EMPAVELI (N=41) n (%)	Eculizumab (N=39) n (%)
<b>General disorders and administration site conditions</b>		
Injection-site reaction*	16 (39)	2 (5)
Fatigue*	5 (12)	9 (23)
Chest pain*	3 (7)	1 (3)
<b>Infections and infestations</b>		
Infections*	12 (29)	10 (26)
Respiratory tract infection*	6 (15)	5 (13)
Viral Infection*	5 (12)	3 (8)
<b>Gastrointestinal disorders</b>		
Diarrhea	9 (22)	1 (3)
Abdominal pain*	8 (20)	4 (10)
<b>Musculoskeletal disorders</b>		
Back pain*	3 (7)	4 (10)
<b>Nervous system disorders</b>		
Headache	3 (7)	9 (23)
<b>Vascular disorders</b>		
Systemic hypertension*	3 (7)	1 (3)

\*The following terms were combined:

**Abdominal pain** includes: abdominal pain upper, abdominal discomfort, abdominal pain, abdominal pain lower, abdominal tenderness, epigastric discomfort

**Back pain** includes: back pain, sciatica

**Chest pain** includes: chest discomfort, non-cardiac chest pain, musculoskeletal chest pain, chest pain

**Fatigue** includes: asthenia, lethargy, fatigue

**Infections** include: oral herpes, bacterial infection, fungal infection, gastrointestinal infection, gastrointestinal viral infection, influenza-like illness, nasopharyngitis, pulpitis dental, rhinitis, tonsillitis, tonsillitis bacterial, vulvovaginal mycotic infection, hordeolum, sepsis, furuncle, otitis externa, viral respiratory tract infection, gastroenteritis, upper respiratory tract infection, bronchitis, ear infection, respiratory tract infection, rhinovirus infection, sinusitis, urinary tract infection

**Injection-site reaction** includes: injection-site erythema, injection-site reaction, injection-site swelling, injection-site induration, injection-site bruising, injection-site pain, injection-site pruritus, vaccination-site reaction, administration-site swelling, injection-site hemorrhage, injection-site edema, injection-site warmth, administration-site pain, application-site pain, injection-site mass, injection-site rash, vaccination-site pain

**Respiratory tract infection** includes: influenza-like illness, nasopharyngitis, rhinitis, tonsillitis, viral upper respiratory tract infection, upper respiratory tract infection, respiratory tract infection, sinusitis

**Systemic hypertension** includes: hypertension

**Viral infection** includes: oral herpes, gastrointestinal viral infection, viral upper respiratory tract infection, rhinovirus infection

Clinically relevant adverse reactions in less than 5% of patients include:

- Intestinal ischemia

- Biliary sepsis
- Hypersensitivity pneumonitis

After the randomized control period, 77 patients continued the study, and all were treated with EMPAVELI monotherapy at the recommended dosing regimen for up to 48 weeks. Serious adverse reactions were reported in 18 patients (23%). Additional adverse reactions reported in >5% of patients treated with EMPAVELI during the open-label part of the study compared to the randomized controlled part in Table 1 were cough (12%), arthralgia (8%), oropharyngeal pain (8%), pyrexia (8%), pain in extremity (7%), thrombocytopenia (7%), abdominal distension (5%), acute kidney injury (5%), anxiety (5%), and myalgia (5%). One patient (1%) died due to COVID-19 infection.

#### Description of Select Adverse Reactions

##### *Injection-Site Reactions*

Injection/infusion-site reactions (e.g., erythema, swelling, induration, pruritis, and pain) have been reported during Study APL2-302. These reactions were mild or moderate in severity.

##### *Diarrhea*

Seventeen cases of diarrhea have been reported during the 48 weeks. Fifteen of the cases were mild and two were moderate.

#### *Study in Complement-Inhibitor Naïve Adult Patients with PNH (Study APL2-308)*

The data described below reflect the exposure in adult patients with PNH who received EMPAVELI (n=46) or the control arm (supportive care excluding complement inhibitors) (n=18) in Study APL2-308 [see *Clinical Studies (14.1)*]. One patient (2%) who received EMPAVELI died due to septic shock. Serious adverse reactions were reported in 6 (13%) patients with PNH receiving EMPAVELI. The most common adverse reaction (≥10%) in patients treated with EMPAVELI were injection site reactions, infections, viral infection, pain in extremity, hypokalemia, arthralgia, dizziness, abdominal pain, rash, and headache.

Table 2 describes the adverse reactions that occurred in ≥5% of patients treated with EMPAVELI in Study APL2-308.

**Table 2: Adverse Reactions Reported in ≥5% of Patients Treated with EMPAVELI in Study APL2-308**

Adverse Reaction	EMPAVELI (N=46) n (%)	Control Arm <sup>a</sup> (N=18) n (%)
	Exposure Adjusted Rate (per 100 pt yrs)	Exposure Adjusted Rate (per 100 pt yrs)
<b>General disorders and administration site conditions</b>		
Injection-site reaction*	12 (26) 42	0 0
Pyrexia	4 (9) 14	0 0
Peripheral edema*	3 (7) 11	0 0
<b>Infections and Infestations</b>		
Infections*	9 (20) 32	4 (22) 74
Viral infection*	6 (13) 21	2 (11) 37

Adverse Reaction	EMPAVELI (N=46) n (%)	Control Arm <sup>a</sup> (N=18) n (%)
	Exposure Adjusted Rate (per 100 pt yrs)	Exposure Adjusted Rate (per 100 pt yrs)
<b>Musculoskeletal and connective tissue disorders</b>		
Pain in extremity	6 (13) 21	0 0
Arthralgia	5 (11) 18	0 0
Musculoskeletal pain	3 (7) 11	0 0
<b>Metabolism and nutrition disorders</b>		
Hypokalemia	6 (13) 21	2 (11) 37
<b>Nervous system disorders</b>		
Dizziness	5 (11) 18	0 0
Headache	5 (11) 18	0 0
Somnolence	3 (7) 11	0 0
<b>Gastrointestinal disorders</b>		
Abdominal pain*	5 (11) 18	1 (6) 18
<b>Skin and subcutaneous tissue disorders</b>		
Rash*	5 (11) 18	0 0
Ecchymosis	3 (7) 11	0 0
Erythema	3 (7) 11	0 0
<b>Blood and lymphatic system disorders</b>		
Thrombocytopenia	3 (7) 11	1 (6) 18
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough*	4 (9) 14	0 0
Epistaxis	3 (7) 11	0 0
<b>Investigations</b>		
Blood creatinine increased	3 (7) 11	0 0

<sup>a</sup>Control Arm = supportive care (excluding complement inhibitors)

EMPAVELI (N=46) group includes patients who received EMPAVELI at any point during the study, including patients randomized to EMPAVELI (N=35) and patients randomized to the control arm and crossed over to EMPAVELI treatment (N=11).

\*The following terms were combined:

**Infections** include: acne pustular, anal abscess, cellulitis, gastroenteritis, helicobacter gastritis, hordeolum, nasopharyngitis, esophageal candidiasis, pharyngitis, septic shock, tuberculosis, upper respiratory tract infection, urinary tract infection enterococcal, vaginal infection, pneumocystitis jirovecii pneumonia, pulmonary tuberculosis, urinary tract infection

**Abdominal pain** includes: abdominal pain, abdominal pain upper.

**Injection site reaction** includes: injection site bruising, injection site hemorrhage, injection site swelling, application site reaction, infusion site pruritus, injection site erythema, injection site rash, puncture site reaction.

**Viral infection** includes: viral infection, covid-19, covid-19 pneumonia, coronavirus test positive, herpes virus, influenza

**Peripheral edema** includes: peripheral swelling, edema peripheral

**Headache** includes: headache, migraine

**Rash** includes: rash, maculo-papular rash, dermatitis

**Cough** includes: cough, allergic cough

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are insufficient data on EMPAVELI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH in pregnancy (*see Clinical Considerations*). The use of EMPAVELI may be considered following an assessment of the risks and benefits.

Treatment of pregnant cynomolgus monkeys with pegcetacoplan at a subcutaneous dose of 28 mg/kg/day (2.9 times human exposure based on AUC) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths compared to controls (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Clinical Considerations

##### *Disease-associated maternal and/or fetal/neonatal risk*

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

#### Data

##### *Animal Data*

Animal reproduction studies with pegcetacoplan were conducted in cynomolgus monkeys. Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times human exposure based on AUC) from the gestation period through parturition resulted in a statistically significant increase in abortions and stillbirths compared to controls. No increase in abortions or stillbirths occurred at a dose of 7 mg/kg/day (1.3 times human exposure based on AUC). No maternal toxicity or teratogenic effects were observed in offspring delivered at term. No developmental effects were observed in infants up to 6 months postpartum. Systemic exposure to pegcetacoplan of less than 1% of maternal levels was detected in fetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester.

### 8.2 Lactation

#### Risk Summary

It is not known whether pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. There are no data on the effects of pegcetacoplan on milk production. Pegcetacoplan is present in milk of lactating monkeys (*see Animal Data*). Since many medicinal products are secreted into human milk, and because of the potential for serious adverse reaction in a breastfeeding child, breastfeeding should be discontinued during treatment and for 40 days after the last dose.



## Data

### Animal Data

Pegcetacoplan was detectable in milk of lactating monkeys at less than 1% concentration of serum levels but was not detectable in the serum of nursing infants.

## 8.3 Females and Males of Reproductive Potential

### Contraception

#### Females

EMPAVELI may cause embryo-fetal harm when administered to pregnant women [see *Use in Specific Populations* (8.1)]. Pregnancy testing is recommended for females of reproductive potential prior to treatment with EMPAVELI. Advise female patients of reproductive potential to use effective contraception during treatment with EMPAVELI and for 40 days after the last dose.

## 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

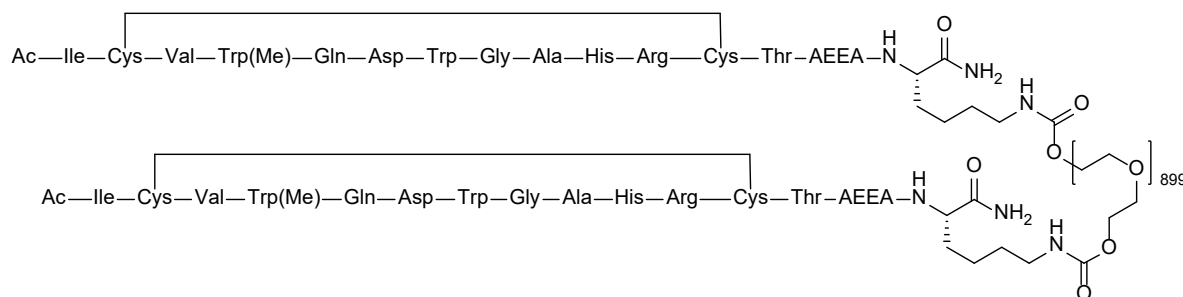
## 8.5 Geriatric Use

Clinical studies of EMPAVELI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between geriatric and younger patients.

## 11 DESCRIPTION

EMPAVELI contains pegcetacoplan, a complement inhibitor. Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kiloDalton (kDa) PEG molecule. The peptide portions of pegcetacoplan contain 1-methyl-L-tryptophan (Trp(Me)) in position 4 and amino(ethoxyethoxy)acetic acid (AEEA) in position 14.

The molecular weight of pegcetacoplan is approximately 43.5 kDa. The molecular formula is  $C_{1970}H_{3848}N_{50}O_{947}S_4$ . The structure of pegcetacoplan is shown below.



EMPAVELI injection is a sterile, clear, colorless to slightly yellowish aqueous solution for subcutaneous use and is supplied in a 20-mL single-dose vial. Each 1 mL of solution contains 54 mg of pegcetacoplan, 41 mg of sorbitol, 0.384 mg of glacial acetic acid, 0.490 mg of sodium acetate trihydrate, and Water for Injection USP. EMPAVELI may also contain sodium hydroxide and/or additional glacial acetic acid for adjustment to a target pH of 5.0.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Pegcetacoplan 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). Pegcetacoplan acts proximally in the complement cascade controlling both C3b-mediated EVH and terminal complement-mediated IVH.

## 12.2 Pharmacodynamics

In patients with PNH administered multiple doses of pegcetacoplan, the mean C3 concentration increased from 0.94 g/L at baseline to 3.80 g/L at Week 16 and sustained through Week 48 (Study APL2-302). In study APL2-308, the mean C3 concentration increased from 0.95 g/L at baseline to 3.56 g/L at Week 26 [see *Clinical Studies (14.1)*].

The percentage of PNH Type II + III RBCs increased from 66.2% at baseline to 93.9% at Week 16 and sustained through Week 48 (Study APL2-302). In Study APL2-308, the mean percentage of PNH Type II + III RBCs increased from 42.4% at baseline to 90.0% at Week 26.

The mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 17.8% at baseline to 0.20% at Week 16 and sustained through Week 48 (Study APL2-302). In Study APL2-308, the mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 2.85% at baseline to 0.09% at Week 26.

### Cardiac Electrophysiology

At the recommended dose of EMPAVELI, no large mean increases in QTc interval (i.e., greater than 20 msec) were observed.

## 12.3 Pharmacokinetics

In patients with PNH, the serum pegcetacoplan concentrations achieved steady-state approximately 4 to 6 weeks following the first dose. The exposure of pegcetacoplan increased proportionally over a dose range from 45 to 1,440 mg (0.04 to 1.33 times the approved recommended dose). The mean (CV%) trough serum concentration observed at Week 16 was 706 (15.1%) mcg/mL and sustained through Week 48 (Study APL2-302). In Study APL2-308, mean (CV%) trough serum concentration was 744 (25.5%) mcg/mL at Week 26.

### Absorption

The median  $T_{max}$  of pegcetacoplan is between 108 and 144 hours (4.5 to 6.0 days) after a single dose.

### Distribution

The mean (CV%) volume of distribution of pegcetacoplan is approximately 3.98 L (32%) in patients with PNH.

### Elimination

The estimated mean (CV%) of clearance (CL) is 0.36 L/day (30%) and median effective half-life of elimination ( $t_{1/2}$ ) is 8.6 days in patients with PNH.

### Metabolism

Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathways.

### Specific Populations

There were no clinically significant differences on the pharmacokinetics of pegcetacoplan based on age (19 to 81 years old), sex, race (Asian vs. non-Asian), renal impairment, and hepatic function as evaluated by total bilirubin (0.06-8.8 mg/dL), albumin (3.0-5.5 g/dL), aspartate aminotransferase (6.0-302 IU/L), or alanine aminotransferase (4.0-209 IU/L).

## 12.6 Immunogenicity

There is insufficient information to characterize the anti-drug antibody response to EMPAVELI and the effects of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of pegcetacoplan products.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of pegcetacoplan have not been conducted.

Pegcetacoplan was not mutagenic when tested in an *in vitro* bacterial reverse mutation (Ames) and was not genotoxic in an *in vitro* assay in human TK6 cells or in an *in vivo* micronucleus assay in mice.

Effects of pegcetacoplan on fertility have not been studied in animals. There were no microscopic abnormalities in male or female reproductive organs in toxicity studies in rabbits and monkeys.

### 13.2 Animal Toxicology and/or Pharmacology

In toxicology studies in rabbits and cynomolgus monkeys, epithelial vacuolation and infiltrates of vacuolated macrophages were observed in multiple tissues, including the renal tubules, following daily subcutaneous doses of pegcetacoplan up to 7 times the human dose. These findings are attributable to uptake of the PEG moieties of pegcetacoplan. Renal degeneration was observed microscopically in rabbits at exposures ( $C_{max}$  and AUC) less than those for the human dose, and in monkeys at exposures approximately 2.7-fold those for the human dose. The clinical significance of these findings is uncertain.

## 14 CLINICAL STUDIES

### 14.1 Paroxysmal Nocturnal Hemoglobinuria

The efficacy and safety of EMPAVELI in patients with PNH were assessed in two open-label, randomized-controlled Phase 3 studies: Study APL2-302 (NCT03500549) and Study APL2-308 (NCT04085601). All patients who completed the studies were eligible to enroll in a separate long-term extension study.

In both studies, patients were vaccinated against *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B (Hib), either within 2 years prior to Day 1 or within 2 weeks after starting treatment with EMPAVELI. Patients vaccinated after initiation of treatment with EMPAVELI received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In addition, prophylactic antibiotic therapy was administered at the discretion of the investigator in accordance with local treatment guidelines for patients with PNH receiving treatment with a complement inhibitor.

A dose of 1,080 mg twice weekly was used for patients randomized to the EMPAVELI group of each study. 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.

#### *Study in Complement-Inhibitor Experienced Adult Patients with PNH (Study APL2-302)*

The study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with Hb levels less than 10.5 g/dL.

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 eculizumab. Patients were then randomized in a 1:1 ratio to receive either 1,080 mg of EMPAVELI twice weekly or their current dose of eculizumab through the duration of the 16-week randomized controlled period (RCP).

Randomization was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28 ( $<4$ ;  $\geq 4$ ) and platelet count at screening ( $<100,000/\text{mm}^3$ ;  $\geq 100,000/\text{mm}^3$ ). Following completion of the RCP, all patients entered a 32-week open-label period (OLP) and received monotherapy with EMPAVELI. Patients initially randomized to eculizumab entered a second 4-week run-in period during which they received EMPAVELI in addition to eculizumab before continuing on to receive EMPAVELI monotherapy. All patients who completed the 48-week period were eligible to enroll in a separate long-term extension study.

A total of 80 patients were randomized to receive treatment, 41 to EMPAVELI and 39 to eculizumab. Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 2). The median times from PNH diagnosis to Day -28 were 6.0 and 9.7 years, respectively, for EMPAVELI and eculizumab. The baseline mean total PNH RBC clone sizes (Type III) were 47% for EMPAVELI and 50% for eculizumab. Twenty-nine percent and 23% of patients had a history of major adverse vascular events, and 37% and 26% had a history of thrombosis for patients receiving EMPAVELI or eculizumab, respectively. Within 28 days prior to the first dose of EMPAVELI or eculizumab, respectively, 34% and 31% of patients used anti-thrombotic agents (anti-platelet and/or anticoagulants). During Study APL2-302, 37% and 36% of patients on EMPAVELI and eculizumab, respectively, used antithrombotic agents. A total of 38 patients in the group treated with EMPAVELI and 39 patients in the eculizumab group completed the 16-week RCP and continued into the 32-week OLP. Because of adverse reactions of hemolysis, 3 patients were discontinued from the EMPAVELI group during the RCP. Two out of 41 patients in the EMPAVELI group needed the dose adjustment to 1,080 mg every 3 days.

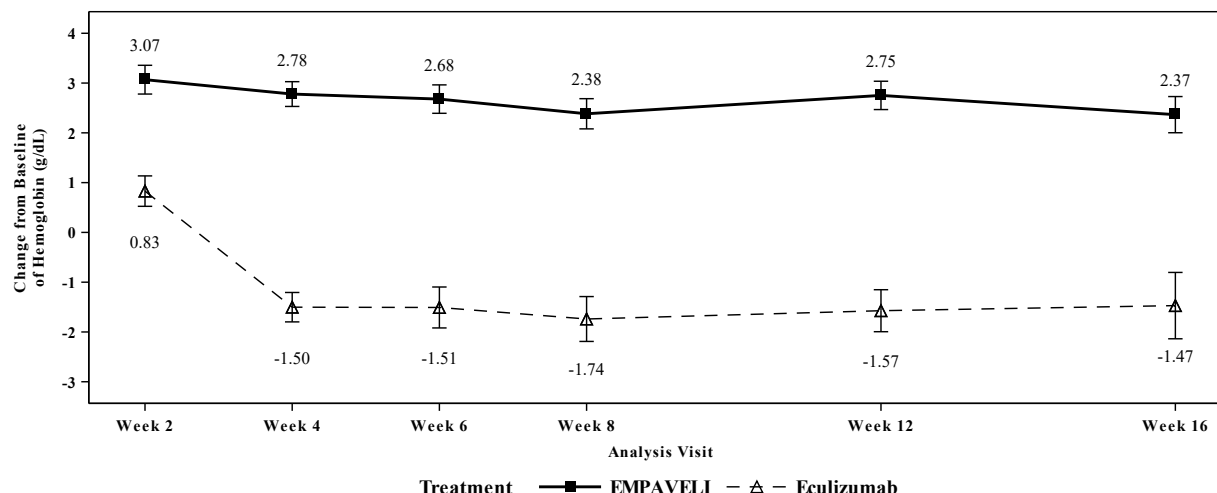
**Table 3: Patient Baseline Demographics and Characteristics in Study APL2-302**

Parameter	Statistics	EMPAVELI (N=41)	Eculizumab (N=39)
Age (years)	Mean (SD)	50.2 (16.3)	47.3 (15.8)
Sex			
Female	n (%)	27 (65.9)	22 (56.4)
Race			
Asian	n (%)	5 (12.2)	7 (17.9)
Black or African American	n (%)	2 (4.9)	0
White	n (%)	24 (58.5)	25 (64.1)
Other	n (%)	0	1 (2.6)
Not reported	n (%)	10 (24.4)	6 (15.4)
Ethnicity			
Hispanic or Latino	n (%)	2 (4.9)	1 (2.6)
Not Hispanic or Latino	n (%)	29 (70.7)	32 (82.1)
Not reported	n (%)	10 (24.4)	6 (15.4)
Hemoglobin level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
Absolute reticulocyte count (10 <sup>9</sup> cells/L)	Mean (SD)	218 (75.0)	216 (69.1)
LDH level (U/L)	Mean (SD)	257.5 (97.7)	308.6 (284.8)
Number of transfusions in last 12 months prior to Day -28	Mean (SD)	6.1 (7.3)	6.9 (7.7)
<4	n (%)	20 (48.8)	16 (41.0)
≥4	n (%)	21 (51.2)	23 (59.0)

The efficacy of EMPAVELI was based on change from baseline to Week 16 (during RCP) in hemoglobin level. Baseline was defined as the average of measurements recorded prior to taking the first dose of EMPAVELI. Supportive efficacy data included transfusion avoidance, defined as the proportion of patients who did not require a transfusion during the RCP, and change from baseline to Week 16 in absolute reticulocyte count (ARC).

EMPAVELI was superior to eculizumab for the change from baseline in hemoglobin level at Week 16 ( $p<0.0001$ ). The adjusted mean change from baseline in hemoglobin level was 2.37 g/dL in the group treated with EMPAVELI versus -1.47 g/dL in the eculizumab group (Figure 1), demonstrating an adjusted mean increase of 3.84 g/dL with EMPAVELI compared to eculizumab at Week 16 (95% CI, 2.33-5.34).

**Figure 1: Adjusted Mean ( $\pm$  SE) Change from Baseline to Week 16 in Hemoglobin (g/dL) in Study APL2-302\***



\*Treatment effect estimates from a mixed model are shown. The mixed model contained the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.

Non-inferiority was demonstrated in the endpoints of transfusion avoidance and change from baseline in ARC at Week 16.

The adjusted means, treatment differences, and confidence intervals (CIs) for additional efficacy results are shown in Table 4.

**Table 4: Additional Efficacy Results at Week 16 in Study APL2-302**

	EMPAVELI (N=41)	Eculizumab (N=39)	Difference (95% CI)
<b>Transfusion avoidance, n (%)</b>	35 (85%)	6 (15%)	63%* (48%, 77%)
<b>Change from baseline in ARC (<math>10^9</math> cells/L), LS<sup>†</sup> mean (SE)<sup>‡</sup></b>	-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.

<sup>†</sup>LS = Least square

<sup>‡</sup>SE = Standard error

Efficacy was generally similar across subgroups based on sex, race, and age.

All 77 patients who completed the RCP entered the 32-week OLP, during which all patients received EMPAVELI, resulting in a total exposure of up to 48 weeks. Between Week 16 and Week 48, 10 patients discontinued the study, all due to adverse reactions, and thirteen patients had a dose adjustment to 1,080 mg every three days. The efficacy results at Week 48 were generally consistent with those at Week 16.

#### *Study in Complement-Inhibitor Naïve Adult Patients with PNH (Study APL2-308)*

Study APL2-308 enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrollment and with Hb levels less than the lower limit of normal (LLN). Eligible patients were randomized in a 2:1 ratio to receive EMPAVELI or supportive care [excluding complement inhibitors (e.g., transfusions, corticosteroids, supplements such as iron, folate, and vitamin B<sub>12</sub>), hereafter referred to as the control arm] through the duration of the 26-week treatment period. Randomization was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28

(<4; ≥4). At any point during the study, a patient assigned to the control arm treatment group who had Hb levels ≥2 g/dL below baseline or presented with a PNH associated thromboembolic event was offered cross-over to EMPAVELI for the remainder of the study.

A total of 53 patients were randomized, 35 to EMPAVELI and 18 to the control arm. Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 4). The mean times from PNH diagnosis to Day 1 were 5.7 and 5.5 years, respectively, for EMPAVELI and the control arm. The baseline mean total PNH RBC clone sizes (Type III) were 31% for EMPAVELI and 28% for the control arm. In the EMPAVELI group, 2.9% of patients had a history of major adverse vascular events. Two patients (5.7%) in the EMPAVELI group and 3 patients (16.7%) in the control arm group had a history of at least 1 type of thrombosis. Within 28 days prior to the first dose of EMPAVELI or the control arm, respectively, 17.1% and 27.8% of patients used anti-thrombotic agents (anti-platelet and/or anticoagulants). During Study APL2-308, 8.6% and 0% of patients on EMPAVELI and the control arm, respectively, used antithrombotic agents. Eleven of 18 patients randomized to the control transitioned to cross-over therapy with EMPAVELI due to a decreased Hb level ≥2 g/dL below baseline. Three patients treated with EMPAVELI required dose adjustment to 1,080 mg every 3 days. Three patients (5.7%; two patients in the EMPAVELI group and one patient in the control arm group) discontinued the study, none due to an adverse reaction.

**Table 5: Patient Baseline Demographics and Characteristics in Study APL2-308**

Parameter	Statistics	EMPAVELI (N=35)	Control Arm <sup>a</sup> (N=18)
Age (years)	Mean (SD)	42.2 (12.7)	49.1 (15.6)
Sex			
Female	n (%)	16 (45.7)	8 (44.4)
Race			
American Indian or Alaska Native	n (%)	9 (25.7)	2 (11.1)
Asian	n (%)	23 (65.7)	16 (88.9)
Black or African American	n (%)	2 (5.7)	0
Other	n (%)	1 (2.9)	0
Ethnicity			
Hispanic or Latino	n (%)	12 (34.3)	2 (11.1)
Not Hispanic or Latino	n (%)	23 (65.7)	16 (88.9)
Hemoglobin level (g/dL)	Mean (SD)	9.4 (1.4)	8.7 (0.8)
Absolute reticulocyte count (10 <sup>9</sup> cells/L)	Mean (SD)	230.2 (81.0)	180.3 (109.1)
LDH level (U/L)	Mean (SD)	2151.0 (909.4)	1945.9 (1003.7)
Number of transfusions in last 12 months prior to Day -28	Mean (SD)	3.9 (4.4)	5.1 (5.0)
<4	n (%)	21 (60.0)	8 (44.4)
≥4	n (%)	14 (40.0)	10 (55.6)

<sup>a</sup>Control Arm = supportive care (excluding complement inhibitors)

The efficacy of EMPAVELI was based on the percentage of patients achieving hemoglobin stabilization, defined as avoidance of a >1 g/dL decrease in hemoglobin levels from baseline in the absence of transfusion, and the change from baseline in LDH level. Supportive efficacy data included change from baseline in absolute reticulocyte count (ARC), change from baseline in hemoglobin, and transfusion avoidance, defined as the proportion of patients who did not require a transfusion through Week 26. Baseline was defined as the average of measurements recorded prior to taking the first dose of EMPAVELI or prior to randomization to the control arm treatment group.

Efficacy results are shown in Table 6 below.

**Table 6: Efficacy Results During the 26-Week Study in Study APL2-308**

	<b>EMPAVELI (N=35)</b>	<b>Control Arm<sup>a</sup> (N=18)</b>	<b>Difference (95% CI) p-value</b>
<b>Hemoglobin Stabilization<sup>§</sup></b> (n, %)	30 (85.7%)	0 (0%)	73% (57%, 89%) p<0.0001*
<b>Change from Baseline in LDH<sup>b</sup> (LS<sup>†</sup> Mean CFB, SE<sup>‡</sup>)</b>	-1870 (101.0)	-400 (313.0)	-1470 (-2113.4, -827.3) p<0.0001
<b>Change from baseline in ARC<sup>b</sup></b> (LS <sup>†</sup> Mean CFB, SE <sup>‡</sup> )	-123 (9.2)	-19 (25.2)	-103 (-158.9, -48.7) p = 0.0002
<b>Change from baseline in Hb<sup>b</sup></b> (LS <sup>†</sup> Mean CFB, SE <sup>‡</sup> )	2.9 (0.38)	0.3 (0.76)	2.7 (0.99, 4.35) p = 0.0019
<b>Transfusion Avoidance<sup>§</sup></b> (n, %)	32 (91%)	1 (6%)	72% (56%, 89%) p<0.0001*

<sup>a</sup>Control Arm = supportive care (excluding complement inhibitors)

<sup>b</sup>The post baseline missing values (including the values after cross-over from the control arm) are imputed using a multiple imputation method.

Data collected after cross-over from the control arm is excluded in analyses.

<sup>§</sup>Patients who crossed over from the control arm group to the EMPAVELI group, withdrew from the study, or were lost to follow up are considered as failing to achieve the criteria.

\*p-value is obtained by stratified Cochran-Mantel-Haenszel test.

<sup>†</sup>LS = Least square

<sup>‡</sup>SE = Standard error

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

EMPAVELI injection is a clear, colorless to slightly yellowish aqueous solution for subcutaneous infusion supplied as 1,080 mg/20 mL (54 mg/mL) solution in 20-mL single-dose vials.

EMPAVELI is available in 20-mL single-dose vials individually packaged in cartons that are supplied in 8-count convenience cartons. NDC 73606-010-01.

### Storage and Handling

Store vials of EMPAVELI refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not use beyond the expiration date stamped on the carton.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

### Serious Infections Caused by Encapsulated Bacteria

Advise patients of the risk of serious infection. Inform patients that they are required to receive vaccinations against encapsulated bacteria at least 2 weeks prior to receiving the first dose of EMPAVELI if they have not been previously vaccinated. They are required to be revaccinated according to current medical guidelines for encapsulated bacteria while on EMPAVELI therapy. Inform patients that vaccination may not prevent serious infection and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms include the following:

- fever with or without shivers or the chills
- fever and a rash
- shortness of breath
- extreme pain or discomfort
- headache with nausea or vomiting
- high heart rate
- headache and a fever
- headache with a stiff neck or stiff back
- confusion
- muscle aches with flu-like symptoms
- clammy skin
- eyes sensitive to light

Inform patients that they will be given a Patient Safety Card for EMPAVELI that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to seek immediate medical evaluation.

#### Anaphylaxis and infusion-related reactions

Advise patients of the risk of anaphylaxis and infusion-related reactions. Inform patients that anaphylaxis is life-threatening and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms include the following:

- difficulty breathing including shortness of breath and wheezing
- swollen tongue or throat
- feeling faint
- rapid heart rate
- skin reactions, including hives and itching
- nausea or vomiting
- confusion and anxiety
- dizziness or fainting

#### Discontinuation

Inform patients with PNH that they may develop hemolysis due to PNH when EMPAVELI is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following discontinuation of EMPAVELI.

Inform patients who discontinue EMPAVELI to keep the Patient Safety Card with them for 2 months after the last dose of EMPAVELI, because the increased risk of serious infection persists for several weeks following discontinuation of EMPAVELI.

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Manufactured For:  
Apellis Pharmaceuticals, Inc.  
100 Fifth Avenue  
Waltham, MA 02451

For patent information: [www.apellis.com/productpatent](http://www.apellis.com/productpatent)

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