

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}**EMPAVELI™**

Pegcetacoplan injection

Solution, 1080 mg / 20 mL (54 mg/mL) for subcutaneous infusion use

Selective immunosuppressants

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EMPAVELI™ (pegcetacoplan) is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have an inadequate response to, or are intolerant of, a C5 inhibitor.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): EMPAVELI may be administered to patients with PNH over 65 years of age. Although there were no apparent age-related differences observed in clinical studies, the number of patients over 65 years of age was not sufficient to determine whether they respond differently from younger subjects. There is no evidence indicating any special precautions are required for treating an elderly population.

2 CONTRAINDICATIONS

EMPAVELI is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- who have unresolved serious infection caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* (see [7 WARNINGS AND PRECAUTIONS, Serious Infections caused by Encapsulated Bacteria](#)).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Due to its mechanism of action, the use of EMPAVELI may predispose individuals to serious infections caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* (see [7 WARNINGS AND PRECAUTIONS, Serious Infections Caused by Encapsulated Bacteria](#)).

- Comply with the most current National Advisory Committee on Immunization (NACI) recommendations for vaccinations against encapsulated bacteria in patients with complement deficiencies.
- Patients must be vaccinated against encapsulated bacteria at least 2 weeks prior to initiating EMPAVELI, unless the risks of delaying EMPAVELI therapy outweigh the risks of developing a serious infection.
- Patients who initiate treatment with EMPAVELI less than 2 weeks after vaccination must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
- Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and treat immediately if infection is suspected.
- EMPAVELI is only available through a controlled distribution program under which prescribers must enrol patients and confirm vaccination against encapsulated bacteria. Prescribers must also counsel patients about the risk of serious infection and provide them with the patient guide and patient card. Information about the EMPAVELI controlled distribution program is available at www.empaveli.ca/HCP.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Therapy should be initiated under the supervision of a healthcare professional experienced in the management of patients with hematological disorders.

Vaccinate patients according to current NACI guidelines to reduce the risk of serious infection (see [7 WARNINGS AND PRECAUTIONS, Serious Infections Caused by Encapsulated Bacteria](#)).

Patients who initiate treatment with EMPAVELI less than 2 weeks after vaccination must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

4.2 Recommended Dose and Dosage Adjustment

EMPAVELI is administered twice weekly as a 1080 mg subcutaneous infusion with a commercially available syringe system infusion pump that can deliver doses up to 20 mL. The twice weekly dose should be administered on Day 1 and Day 4 of each treatment week (see [4.4 Administration](#)). EMPAVELI can be given by a healthcare professional or administered by the patient or caregiver following proper instruction. Infuse EMPAVELI in the abdomen, thighs, hips, or upper arms.

PNH is a chronic disease and treatment with EMPAVELI is recommended to continue for the patient's lifetime unless the discontinuation is clinically indicated (see [7 Warnings and Precautions](#), EMPAVELI Treatment Discontinuation).

Dosage for patients switching to EMPAVELI from C5 inhibitors

- For the first 4 weeks, EMPAVELI is administered as twice weekly subcutaneous doses of 1080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimize the risk of hemolysis with abrupt treatment discontinuation.
- After 4 weeks, the patient can discontinue C5 inhibitor while continuing on monotherapy with EMPAVELI.

Dose adjustment for EMPAVELI

- The dosing regimen may be changed to 1080 mg every third day (i.e., Day 1, Day 4, Day 7, Day 10, Day 13, and so forth) if a subject has a lactate dehydrogenase (LDH) level greater than 2 × the upper limit of normal (ULN) on twice weekly dosing.
- In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.

No dosage adjustment is required in geriatric patients, patients with renal impairment, or in patients with hepatic impairment (see [7.1.4 Geriatrics](#) and [10.3 Pharmacokinetics, Special Populations and Conditions](#)). EMPAVELI has not been studied in patients with end-stage renal disease requiring hemodialysis.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

EMPAVELI should only be administered via subcutaneous administration using a syringe system infusion pump.

When therapy with EMPAVELI is initiated, a qualified healthcare professional will instruct the patient in infusion techniques, the use of a syringe system infusion pump, the keeping of a treatment record, recognition of possible adverse reactions, and measures to be taken in case these occur.

- 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.
- EMPAVELI is a clear, colourless 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. Infusion sites should be at least 3 inches (7.5 cm) apart from each other. Do not infuse where the skin is tender, bruised, red, or hard. Avoid infusing into tattoos, scars, or stretch marks.
- The typical infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site). The infusion should be started promptly after drawing

EMPAVELI into the syringe. Complete the administration within 2 hours after preparing the syringe.

- Discard any unused portion.

4.5 Missed Dose

If a dose of EMPAVELI is missed, it should be administered as soon as possible, then the regular schedule should be resumed.

5 OVERDOSAGE

No case of overdose of EMPAVELI has been reported during clinical studies.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Form, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients*
Subcutaneous infusion	Solution / 1080 mg/20 mL single-dose vials	glacial acetic acid, sodium acetate trihydrate, sorbitol, water for injection

* May also contain sodium hydroxide and/or additional glacial acetic acid for pH adjustment.

EMPAVELI is a clear, colourless to slightly yellowish sterile aqueous solution.

EMPAVELI is available in the following formats:

- Carton containing 1 x 20 mL (54 mg/mL) single-dose vial

7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#).

Serious Infections caused by Encapsulated Bacteria

EMPAVELI is only available under a controlled distribution program. Information about the EMPAVELI controlled distribution program is available at www.empaveli.ca/HCP.

Due to its mechanism of action, the use of EMPAVELI may predispose individuals to serious infections caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. To reduce the risk of infection, all patients must be

vaccinated against these bacteria according to current local guidelines at least 2 weeks prior to receiving EMPAVELI, unless the risk of delaying therapy with EMPAVELI outweighs the risk of developing an infection. Revaccinate patients in accordance with current local guidelines and recommendations considering the duration of therapy with EMPAVELI. Patients who initiate treatment with EMPAVELI less than 2 weeks after vaccination must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

Vaccination may not be sufficient to prevent serious infection. Consider official guidance on the appropriate use of antibacterial agents. Monitor all patients for early signs of infections caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, evaluate immediately if infection is suspected, and treat with appropriate antibiotics if necessary. Inform patients of these signs and symptoms and that they should seek medical care immediately.

General

Hypersensitivity Reactions

Hypersensitivity reactions have been reported. If a severe hypersensitivity reaction (including anaphylaxis) occurs, discontinue infusion with EMPAVELI immediately and institute appropriate treatment.

EMPAVELI Treatment Discontinuation

If patients with PNH discontinue treatment with EMPAVELI, they should be closely monitored for signs and symptoms of serious intravascular hemolysis. Intravascular hemolysis is identified by elevated LDH levels along with sudden decrease in PNH clone size or hemoglobin (Hb), or reappearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction. If discontinuation of EMPAVELI is necessary, an alternate therapy should be considered because PNH is life-threatening if untreated. Patients should be closely monitored for at least 8 weeks from the last dose of EMPAVELI to detect serious hemolysis and other reactions. In addition, slow weaning should be considered.

Hereditary fructose intolerance

EMPAVELI 1080 mg contains 820 mg sorbitol in each vial.

Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Driving and Operating Machinery

EMPAVELI has no influence on the ability to drive and use machines.

Immune

Immunogenicity

As with all therapeutic peptides, there is a potential for immunogenicity. Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. The available methodology and data on anti-pegcetacoplan antibody formation were not adequate to fully assess the incidence of anti-drug antibodies or their effect on pharmacokinetics, pharmacodynamics, safety, or effectiveness of pegcetacoplan.

Monitoring and Laboratory Tests

PNH Laboratory Monitoring

Patients with PNH receiving EMPAVELI should be monitored regularly for signs and symptoms of hemolysis, including measuring LDH levels, and may require dose adjustment within the recommended dosing schedule (see [4.2 Recommended Dose and Dosage Adjustment](#)).

Effects on Laboratory Tests

There may be interference between silica reagents in coagulation panels and pegcetacoplan that results in artificially prolonged activated partial thromboplastin time (aPTT); therefore, the use of silica reagents in coagulation panels should be avoided.

Polyethylene Glycol (PEG) Accumulation

EMPAVELI is a PEGylated medicinal product. The potential long-term effects of PEG accumulation in the kidneys, the choroid plexus of the brain, and other organs are unknown (see [16 NON-CLINICAL TOXICOLOGY](#)). Regular laboratory testing of renal function is recommended.

Reproductive Health: Female and Male Potential

It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with pegcetacoplan and for at least 8 weeks after the last dose of pegcetacoplan (see [7.1.1 Pregnant Women](#)). For women planning to become pregnant, the use of EMPAVELI may be considered following an assessment of the risks and benefits.

- **Fertility**

Effects of pegcetacoplan upon 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.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data on EMPAVELI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The use of EMPAVELI may be considered following an assessment of the risks and benefits.

Animal reproduction studies with pegcetacoplan were conducted in rats, rabbits, and cynomolgus monkeys. Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times the human steady state AUC) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths compared to controls. No maternal toxicity or teratogenic effects were observed in offspring delivered at term. Additionally, no developmental effects were observed in infants up to 6 months postpartum. Systemic exposure to pegcetacoplan was detected in fetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester (less than 1% of maternal serum levels) (see [16 NON-CLINICAL TOXICOLOGY](#)).

7.1.2 Breast-feeding

It is not known whether pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Pegcetacoplan excretion in milk has been demonstrated in monkeys (less than 1% of maternal serum levels) (see [16 NON-CLINICAL TOXICOLOGY](#)).

It is recommended to discontinue breast-feeding during pegcetacoplan treatment. Breastfeeding should be discontinued during treatment and for 8 weeks after the last dose.

7.1.3 Pediatrics

- **Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

- **Geriatrics (> 65 years of age):** EMPAVELI may be administered to patients with PNH over 65 years of age. Although there were no apparent age-related differences observed in clinical studies, the number of patients over 65 years of age was not sufficient to determine whether they respond differently from younger subjects. There is no evidence indicating any special precautions are required for treating an elderly population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of EMPAVELI in patients with PNH was evaluated in the open-label, randomized, active-controlled, Phase 3 study PEGASUS (Study APL2-302).

A total of 8 serious adverse events (irrespective of causality) were reported in 7 (17.1%) patients treated with EMPAVELI. These included hemolysis in 2 patients (4.9%) and gastroenteritis, bacterial infection, dyspnea, atrial fibrillation, pyrexia and facial paralysis in 1 patient each (2.4%).

The most frequent adverse events ($\geq 10\%$) reported in patients treated with EMPAVELI were diarrhea (22.0%), injection site erythema (17.1%) and hemolysis (12.2%). A total of 3 (7.3%) patients discontinued EMPAVELI due to hemolysis.

In patients treated with EMPAVELI, the most commonly reported adverse reactions ($\geq 5\%$) (as assessed by investigators) were injection site erythema (14.6%), injection site reaction (9.8%), injection site swelling (9.8%) and injection site induration (7.3%). These reactions were mild to moderate in intensity and did not lead to discontinuation of treatment.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)

PEGASUS (APL2-302)

The safety of EMPAVELI (pegcetacoplan) solution for subcutaneous infusion was evaluated in patients with PNH in the PEGASUS study. This was a Phase 3, open-label, randomized, active-controlled, multicentre study in patients ≥ 18 years of age with PNH and Hb levels < 10.5 g/dL (< 105 g/L) despite treatment with a stable dose of eculizumab for at least 3 months prior to the study screening visit. The data described below reflect the exposure of patients with PNH who received EMPAVELI at the recommended dosing regimen of 1080 mg twice weekly for up to 48 weeks, including a 16-week randomized controlled period (RCP) and a 32-week open-label period (OLP). Table 2 describes the adverse reactions as assessed by investigators and reported in $\geq 3\%$ of patients during the RCP in the PEGASUS study.

Table 2 Adverse Reactions as Assessed by Investigators Reported in ≥3% in PNH Patients Treated with EMPAVELI in the PEGASUS Study (APL2-302) – Safety Analysis Set

	RCP	
System Organ Class Preferred Term ^a	EMPAVELI ^b (N = 41) n (%)	Eculizumab ^c (N = 39) n (%)
Blood and lymphatic system disorders		
Hemolysis	2 (4.9)	3 (7.7)
General disorders and administration site conditions		
Injection site erythema	6 (14.6)	0
Injection site reaction	4 (9.8)	0
Injection site swelling	4 (9.8)	0
Injection site induration	3 (7.3)	0

^aMedDRA Version 23.0

^bIncludes ADRs that started during EMPAVELI monotherapy during the RCP.

^cIncludes ADRs that started during eculizumab monotherapy in the RCP.

RCP, Randomized Controlled Period

Additional adverse reactions reported in ≥3% of patients treated with EMPAVELI during the entire 48-week study (N=80) compared to Table 2 were injection site pruritus (6.3%), headache (5.0%) and pyrexia (3.8%).

8.3 Less Common Clinical Trial Adverse Reactions

The less common adverse reactions (as assessed by the investigators) reported between 2% and <3% of patients treated with EMPAVELI in the RCP in the PEGASUS study are shown below.

General disorders and administration site conditions: injection site pruritus and injection site pain (2.4% each)

Gastrointestinal disorders: diarrhea (2.4%)

Nervous system disorders: facial paralysis and heart discomfort (2.4% each)

Infections and infestations: nasopharyngitis (2.4%)

Investigations: bilirubin conjugated increased and weight increased (2.4% each)

Musculoskeletal and connective tissue disorders: neck pain (2.4%)

Skin and subcutaneous tissue disorders: erythema and pigmentation disorder (2.4% each)

Hepatobiliary disorders: hyperbilirubinemia (2.4%)

Vascular disorders: hypertension (2.4%)

Metabolism and nutrition disorders: hypercalcemia (2.4%)

Psychiatric disorders: restlessness (2.4%)

Additional adverse reactions reported between 2 and <3% of patients treated with EMPAVELI during the entire 48-week study (N=80) compared to the RCP were:

Blood and lymphatic system disorders: thrombocytopenia (2.5%)

Infections and infestations: Urinary tract infection (2.5%)

Investigations: alanine aminotransferase increased (2.5%)

8.4 Abnormal laboratory findings

Table 3 summarizes the CTCAE grades 3 and 4 laboratory abnormalities for PNH patients who had normal values at Baseline in the PEGASUS study.

Table 3: CTCAE Grades 3 and 4 Laboratory Abnormalities in the PEGASUS Study (APL2-302) – Safety Analysis Set

Laboratory Parameter	EMPAVELI (N=41) n (%)	ECULIZUMAB (N=39) n (%)
Neutropenia	2 (4.9%)	1 (2.9%)
Thrombocytopenia	2 (4.9%)	2 (5.1%)
Elevated ALT	1 (2.4%)	2 (5.1%)
Elevated AST	0	1 (2.6%)
Elevated total bilirubin	1 (3.0%)	5 (16.7%)
Elevated direct bilirubin	0	8 (25.8%)
Elevated BUN	0	0
Elevated creatinine	0	0

Note: Worst on-study (during the randomized phase) values in patients with normal baseline.

CTC Grades:

Neutrophil count decreased (Grade 3: <1.0 - 0.5 x 10⁹/L, Grade 4: <0.5 x 10⁹/L)

Platelet count decreased (Grade 3: <50.0 - 25.0 x 10⁹/L, Grade 4: <25.0 x 10⁹/L)

Alanine aminotransferase and Aspartate aminotransferase increased
(Grade 3: >5.0 - 20.0 x ULN, Grade 4: >20.0 x ULN)

Blood bilirubin increased (Grade 3: >3.0 - 10.0 x ULN, >10.0 x ULN)

Blood Urea Nitrogen (BUN) (Grade 3: >31 mg/dL)

Creatinine increased (Grade 3: >3.0 - 6.0 x ULN, >6.0 x ULN)

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

No interaction studies have been performed. Based on *in vitro* data, pegcetacoplan has low potential for clinical drug-drug interactions.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

There may be interference between silica reagents in coagulation panels and pegcetacoplan that results in artificially prolonged activated partial thromboplastin time (aPTT); therefore, the use of silica reagents in coagulation panels should be avoided.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

In Study APL2-302, mean C3 concentration increased from 0.94 g/L at baseline to 3.83 g/L at Week 16 in the pegcetacoplan group and was sustained through Week 48. The percentage of PNH Type II + III RBCs increased from 66.8% at baseline to 93.9% at Week 16 and remained elevated through Week 48. The mean percentage of PNH Type II + III RBCs with C3 deposition was decreased from 17.7% at baseline to 0.20% at Week 16 which was sustained through Week 48.

Cardiac Electrophysiology

No specific studies have been conducted to determine the potential for pegcetacoplan to delay cardiac repolarization. Pegcetacoplan showed no inhibition in the human ether-a-go-go gene (hERG) ion channel assay *in vitro*. Analysis of concentration-QTc (QT interval corrected for heart rate) confirmed no large mean increases in QTc interval (i.e., greater than 20 msec) at the recommended dose of EMPAVELI.

10.3 Pharmacokinetics

Steady-state serum concentrations following twice weekly dosing at 1080 mg in patients with PNH were achieved approximately 4 to 6 weeks following the first dose. In Study APL2-302, the mean (%CV) steady-state serum concentrations of pegcetacoplan ranged between 590 (38.9%) to 706 (15.1%) µg/mL in patients treated for 48 weeks. Exposure of pegcetacoplan increased in a dose-proportional manner from 45 to 1440 mg.

Absorption

Pegcetacoplan is administered by subcutaneous infusion and is gradually absorbed into the systemic circulation with a median T_{max} between 108 and 144 hours (4.5 to 6.0 days).

Distribution

The mean (%CV) of central volume of distribution of pegcetacoplan is approximately 3.9 L (35%) in patients with PNH.

Metabolism

Based on its PEGylated peptide structure, the degradation of pegcetacoplan is expected to occur via catabolic pathways into small peptides, amino acids and PEG.

Elimination

Results of a radiolabeled study in cynomolgus monkeys suggest the primary route of elimination of the labelled peptide moiety is via urinary excretion. Although the elimination of PEG was not studied, it is known to undergo renal excretion.

Following multiple subcutaneous dosing of pegcetacoplan, the estimated mean (CV%) of clearance (CL) is 0.015 L/hour (28%) and median effective half-life of elimination ($t_{1/2}$) is 8.0 days in patients with PNH.

Special Populations and Conditions

No impact on the pharmacokinetics of pegcetacoplan was identified with age (19 to 81 years), race (Asian versus non-Asian) and sex based on the results of population pharmacokinetic analysis.

- **Hepatic Insufficiency:** No specific studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of pegcetacoplan. As biotransformation is mainly via catabolism, hepatic impairment is not expected to influence the clearance of pegcetacoplan.
- **Renal Insufficiency:** In a study that enrolled 8 participants with severe renal impairment, defined as creatinine clearance (CrCl) less than 30 mL/min using the Cockcroft-Gault formula (with 4 participants with CrCl less than 20 mL/min), renal impairment had no effect on the pharmacokinetics of pegcetacoplan. There are no available clinical data for the use of pegcetacoplan in patients with end-stage renal disease requiring hemodialysis.

11 STORAGE, STABILITY AND DISPOSAL

Store in the refrigerator (2°C to 8°C). Keep EMPAVELI in its original package to protect from light.

Discard any partially used vial(s) and disposable supplies in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

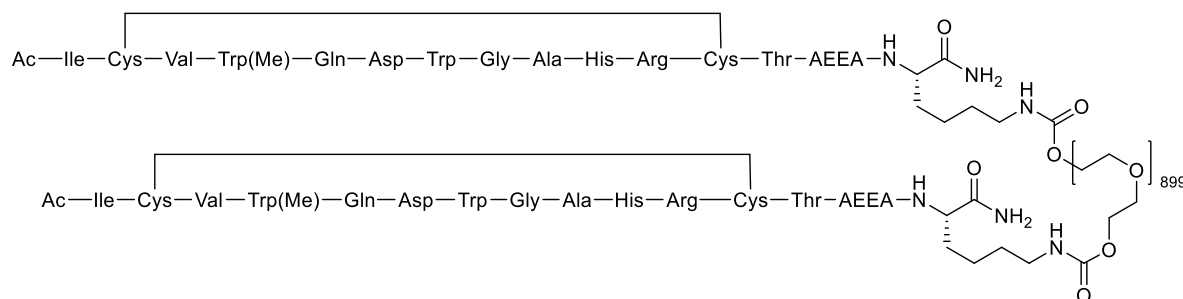
Drug Substance

Proper name: pegcetacoplan

Chemical name: *N*^{6,15},*N*^{6,15'}-[poly(oxyethylene), oxy- α -carbonyl, ω -carbonyl]-bis[N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminy-L-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-L-lysineamide, cyclic(2-12)-disulfide]

Molecular formula and molecular mass: C₁₉₇₀H₃₈₄₈N₅₀O₉₄₇S₄
43.5 kDa

Structural formula:



Physicochemical properties: Pegcetacoplan is a white to off-white solid. Pegcetacoplan exists as the free-base, free of specific counterions. Pegcetacoplan is very soluble in both water and buffer (10 mM acetate buffer, pH 5.0 containing 4.1% sorbitol), and freely soluble in both ethanol and 5% dextrose solution.

At 25 °C, pegcetacoplan displays negligible adsorption of water at moderate relative humidity (RH) levels (i.e., less than 3% water adsorption at RH \leq 65%) and low to moderate water adsorption at high relative humidity levels (i.e., ca 6% water adsorption at 85% RH).

Aqueous solutions of pegcetacoplan (5 mg/mL in unbuffered water) were found to have pH values between 7.0 and 7.5.

Pegcetacoplan is indicated as very hydrophilic with a calculated logP value is -8.0.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)

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

In PEGASUS, 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 Day 1 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.

The dose of EMPAVELI was 1080 mg twice weekly. If required, the dose of EMPAVELI could be adjusted to 1080 mg every 3 days. EMPAVELI was administered as a subcutaneous infusion; the infusion time was approximately 20 to 40 minutes.

PEGASUS (Study APL2-302)

PEGASUS was a Phase 3, randomized, open-label, actively-controlled 16-week study followed by a 32-week open label period (OLP) (NCT03500549). 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 <10.5 g/dL (<105 g/L).

Eligible patients entered a 4-week run-in period during which they received EMPAVELI 1080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomized in a 1:1 ratio to receive either 1080 mg of EMPAVELI twice weekly or their current dose of eculizumab through the duration of the 16-week randomized controlled period (RCP). If required, the dose of EMPAVELI could be adjusted to 1080 mg every 3 days.

Randomization was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28 (<4; ≥4) and platelet count at screening (<100,000/mm³; ≥100,000/mm³). Following completion of the RCP, all patients entered a 32-week open-label period (OLP) and received EMPAVELI for up to 32 weeks (patients who received eculizumab during the RCP entered a 4-week run in period before switching to 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 comparable between

treatment groups (see Table 4 and Table 5). 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. Per protocol 15 subjects had their dose adjusted to 1080 mg every three days. Twelve patients were evaluated for benefit and 8 of the 12 patients demonstrated benefit from the dose adjustment.

Table 4 Summary of Trial Design and Patient Demographics in PNH, PEGASUS Study (APL2-302)

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
APL2-302	Phase 3, multicenter, open-label, randomized, active controlled study in patients previously treated with complement inhibitor therapy	1080 mg/mL, subcutaneous infusion, twice weekly	<u>EMPAVELI</u> n=41 <u>Eculizumab</u> n=39 Total n=80	<u>EMPAVELI</u> 50.2 years (19 – 81) <u>Eculizumab</u> 47.3 years (23 - 78)	<u>EMPAVELI</u> Female 27 (65.9) Male 14 (34.1) <u>Eculizumab</u> Female 22 (56.4) Male 17 (43.6)

Table 5 Patient Baseline Demographics and Characteristics in PNH, PEGASUS (APL2-302)

Parameter	Statistics	EMPAVELI (n=41)	Eculizumab (n=39)
Age (years)	Mean (SD)	50.2 (16.3)	47.3 (15.8)
18-64 years	n (%)	31 (75.6)	32 (82.1)
≥65 years	n (%)	10 (24.4)	7 (17.9)
Sex			
Female	n (%)	27 (65.9)	22 (56.4)
Male	n (%)	14 (34.1)	17 (43.6)
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)
Dose level of eculizumab at baseline			
Every 2 weeks IV 900 mg	n (%)	26 (63.4)	29 (74.4)
Every 11 days IV 900 mg	n (%)	1 (2.4)	1 (2.6)
Every 2 weeks IV 1200 mg	n (%)	12 (29.3)	9 (23.1)
Every 2 weeks IV 1500 mg	n (%)	2 (4.9)	0
Time since diagnosis of PNH (years) to Day -28	Mean (SD)	8.7 (7.4)	11.4 (9.7)
Hb level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
Hb level (g/L)	Mean (SD)	86.9 (10.7)	86.8 (8.9)
Absolute Reticulocyte count (10 ⁹ /L)	Mean (SD)	218 (75.0)	216 (69.1)
LDH level (U/L)	Mean (SD)	257.5 (97.7)	308.6 (284.8)
Total FACIT fatigue score*	Mean (SD)	32.2 (11.4)	31.6 (12.5)
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)
Platelet count at screening (10 ⁹ /L)	Mean (SD)	167 (98.3)	147 (68.8)
<100,000/mm ³	n (%)	12 (29.3)	9 (23.1)
≥100,000/mm ³	n (%)	29 (70.7)	30 (76.9)

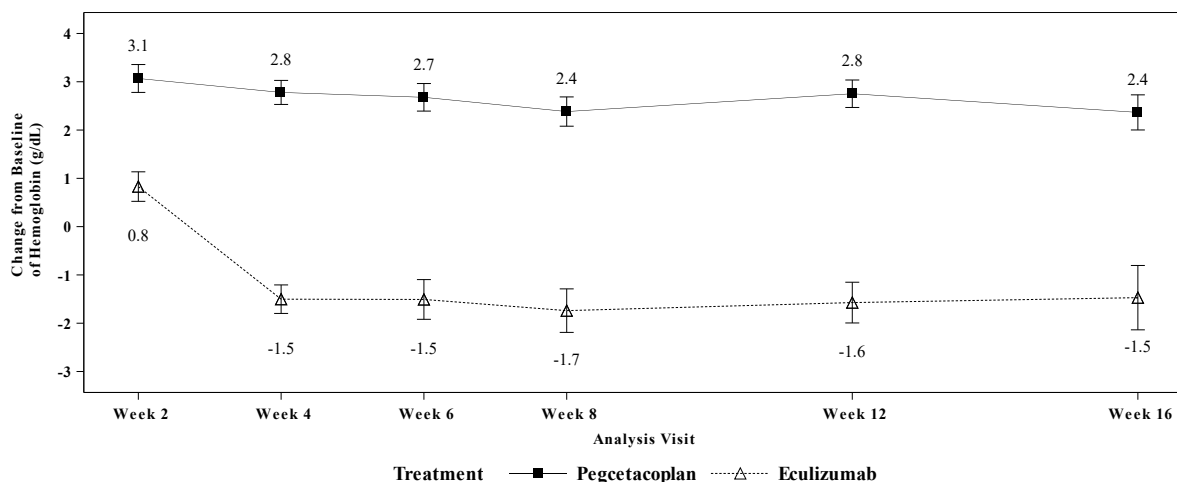
Parameter	Statistics	EMPAVELI (n=41)	Eculizumab (n=39)
PNH RBC clone sizes (Type III)	Mean total (%)	47	50
History of aplastic anemia	n (%)	11 (26.8)	9 (23.1)
History of myelodysplastic syndrome	n (%)	1 (2.4)	2 (5.1)
History of at least one type of Thrombosis	n (%)	15 (36.6)	10 (25.6)

*FACIT Fatigue is measured on a scale of 0-52, with higher values indicating less fatigue.

The primary and secondary efficacy endpoints were assessed at Week 16. The primary efficacy endpoint was change from baseline to Week 16 (during RCP) in Hb level. Baseline was defined as the average of measurements recorded prior to taking the first dose of EMPAVELI. Key secondary efficacy endpoints were 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), LDH level, and FACIT-fatigue scale score.

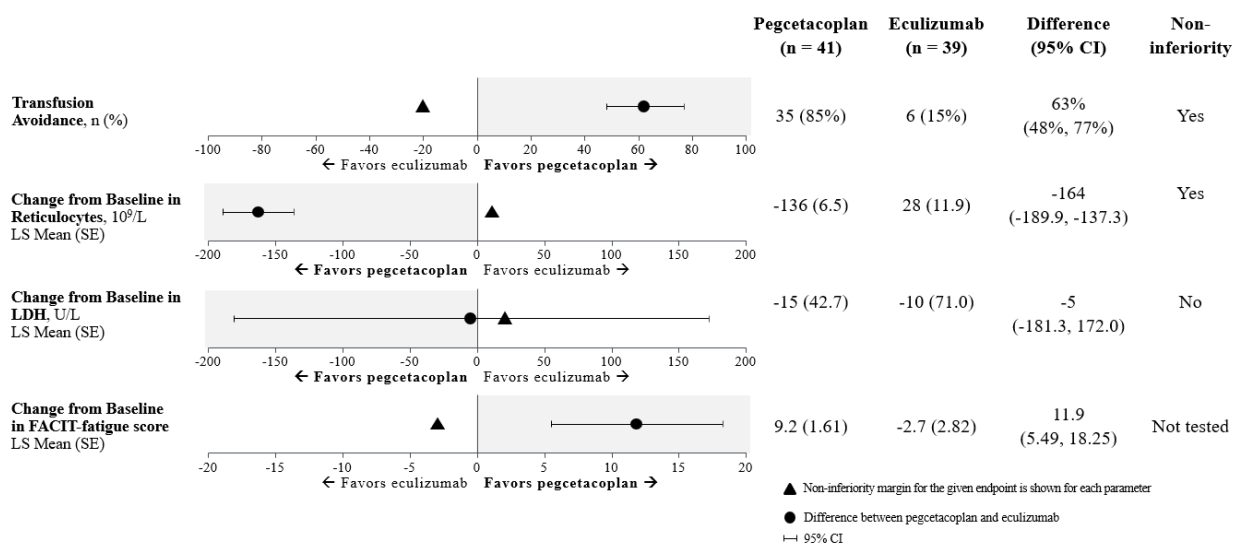
EMPAVELI was superior to eculizumab for the primary endpoint of the Hb change from baseline ($p < 0.0001$). The adjusted mean change from baseline in Hb level was 2.4 g/dL (24 g/L) in the group treated with EMPAVELI versus -1.5 g/dL (-15 g/L) in the eculizumab group, demonstrating an adjusted mean increase of 3.8 g/dL (38 g/L) with EMPAVELI compared to eculizumab at Week 16 (95% CI, 2.33-5.34) (Figure 1). Treatment differences between the EMPAVELI and eculizumab groups were evident as early as Week 2 and persisted throughout the 16-week RCP.

Figure 1 Adjusted Mean (\pm SE) Change from Baseline to Week 16 in Hemoglobin (g/dL), PEGASUS (APL2-302)



Non-inferiority was demonstrated in key secondary endpoints of transfusion avoidance and ARC (see Figure 2). Transfusion avoidance was achieved in 85% of patients in the group treated with EMPAVELI, as compared to 15% in the eculizumab group. In the group treated with EMPAVELI, the adjusted mean change from baseline in ARC was $-136 \times 10^9/\text{L}$ versus $28 \times 10^9/\text{L}$ in the eculizumab group, demonstrating an adjusted mean decrease of $-164 \times 10^9/\text{L}$ compared to eculizumab.

Figure 2 Key Secondary Endpoints Analysis, PEGASUS (APL2-302)



FACIT-fatigue score not tested as LDH did not achieve non-inferiority.

Results were consistent across all supportive analyses of the primary and key secondary endpoints, including all observed data with posttransfusion data included.

In patients treated with EMPAVELI, primary and key secondary efficacy analyses showed no notable differences based on gender, race, or age, however; these results need to be interpreted with caution given small sample sizes.

LDH normalization was achieved in 71% of patients in the group treated with EMPAVELI and in 15% of the eculizumab group. Normalization of ARC was achieved in 78% of patients in the group treated with EMPAVELI and in 3% of the eculizumab group.

A total of 77 patients entered the 32-week OLP, during which all patients received EMPAVELI, resulting in a total exposure of up to 48 weeks. The results at Week 48 were generally consistent with those at Week 16 and support sustained efficacy.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Repeat-dose studies were conducted in rabbits (4 weeks and 6 months) and cynomolgus monkeys (4 weeks and 9 months) with daily subcutaneous doses of pegcetacoplan up to 7 times the human dose (1080 mg twice weekly). Histologic findings were observed in both species at exposures (C_{max} and AUC) lower than those for the human dose and included dose-dependent epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues. These findings are attributable to uptake of the PEG moieties of pegcetacoplan. Reversibility was not demonstrated in the pegcetacoplan animal studies after one month and was not evaluated for a longer duration.

Renal tubular degeneration was observed microscopically in both species at exposures (C_{max} and AUC) less than (rabbit) or comparable (monkey) to those for the human dose after daily administration of pegcetacoplan for 4-weeks and 9 months, to a similar extent. These findings were still observed in the 4-week study in monkeys following a 4-week recovery period. The NOAEL for renal degeneration in monkeys was 7 mg/kg/day (1.4-fold margin for C_{max} and AUC over clinical exposure). The clinical significance and functional consequence of these findings are unknown.

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

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

Reproductive and Developmental Toxicology:

Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of

28 mg/kg/day (2.9 times the human steady state AUC) from gestation day 20 through parturition resulted in a statistically significant increase in abortions or stillbirths compared to controls. No maternal toxicity or teratogenic effects were observed in offspring delivered at term. Additionally, no developmental effects were observed in infants up to 6 months postpartum. Pegcetacoplan was detected in fetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester (exposure was less than 1% of maternal serum levels).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **EMPAVELI™**

Pegcetacoplan injection

Read this carefully before you start taking **EMPAVELI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EMPAVELI**.

Serious Warnings and Precautions

EMPAVELI increases your chance of getting serious infections caused by certain types of bacteria. This includes serious infections caused by the bacteria *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.

- You must be vaccinated against these bacteria at least 2 weeks before your first dose of EMPAVELI, if you have not already had these vaccines in the past.
- If you start EMPAVELI therapy less than 2 weeks after being vaccinated, your healthcare professional will prescribe antibiotics. You must take antibiotics to reduce the risk of infection until 2 weeks after your vaccination.
- You must be monitored for early signs of serious infections (i.e., from *streptococcus pneumoniae*, *neisseria meningitidis*, and *haemophilus influenzae*). Vaccines reduce the risk of serious infections, but do not prevent all serious infections. If you have any of the following symptoms, you should **seek medical care immediately**:
 - fever with or without shivers or the chills
 - fever and a rash
 - headache and a fever
 - headache with nausea or vomiting
 - headache with a stiff neck or stiff back
 - shortness of breath
 - high heart rate
 - extreme pain or discomfort
 - confusion
 - muscle aches with flu-like symptoms
 - clammy skin
 - eyes sensitive to light
- EMPAVELI is only available through a controlled distribution program. Talk to your healthcare professional if you have any questions about this program.

What is EMPAVELI used for?

EMPAVELI is used to treat adult patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) when treatment with another type of PNH medicine called C5 inhibitor has not worked well or was not tolerated well. PNH is a type of disease that affects the blood system.

It is not known if EMPAVELI is safe and effective in children.

How does EMPAVELI work?

EMPAVELI is a medicine that contains the active substance pegcetacoplan. Pegcetacoplan has been designed to attach to the C3 complement protein, which is a part of the body's defence system called the 'complement system'. Pegcetacoplan prevents your body's immune system from destroying your red blood cells.

What are the ingredients in EMPAVELI?

Medicinal ingredients: pegcetacoplan

Non-medicinal ingredients: glacial acetic acid, sodium acetate trihydrate, sorbitol, water for injection.

EMPAVELI comes in the following dosage forms:

Solution for subcutaneous infusion: 1080 mg / 20 mL in a vial

Do not use EMPAVELI if:

- you are allergic to pegcetacoplan or any of the other ingredients of this medicine (see [What are the ingredients in EMPAVELI?](#)).
- you have an infection caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*. See [Serious Warnings and Precautions Box](#) at the beginning of this Patient Medication Information.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EMPAVELI. Talk about any health conditions or problems you may have, including if you:

- have an infection or fever.
- have an intolerance to some sugars or have hereditary fructose intolerance (a rare genetic disorder in which a person cannot break down fructose). EMPAVELI contains sorbitol, a source of fructose.

Other warnings you should know about:

Female patients

Pregnancy and birth control

- Talk to your healthcare professional if you are pregnant or planning to become pregnant. EMPAVELI may harm your unborn baby.
- Females who are able to become pregnant should have a pregnancy test before starting treatment with EMPAVELI.
- Avoid becoming pregnant during treatment with EMPAVELI. Females who are able to become pregnant should use an effective method of birth control during treatment and for at least 8 weeks after your last dose of EMPAVELI.
- Talk to your healthcare professional right away if you become pregnant during treatment.

Breastfeeding

- Talk to your healthcare professional if you are breastfeeding or plan to breastfeed. It is not known if EMPAVELI passes into your breast milk.
- You should not breastfeed during treatment with EMPAVELI and for 8 weeks after the last dose.

Monitoring and laboratory tests

During your treatment with EMPAVELI, your healthcare professional will do regular check-ups. This includes blood tests for lactate dehydrogenase (LDH) levels. Depending on your test results, your healthcare professional may adjust your dose if needed.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with EMPAVELI:

There are no known interactions with EMPAVELI at this time.

Know the medicines you take and the vaccines you receive. Keep a list of them to show your healthcare professional when you get a new medicine.

How to take EMPAVELI:

At least 2 weeks before you start treatment with this medicine, your healthcare professional will review your medical records and may give you one or more vaccinations. If you cannot be vaccinated at least 2 weeks before you start treatment with EMPAVELI, your healthcare professional will prescribe antibiotics. You must take antibiotics to reduce the risk of infection until 2 weeks after your vaccination.

- See the detailed [Instructions for Use](#) that comes with your EMPAVELI for information about how to prepare and infuse your dose of EMPAVELI.

- Your healthcare professional will show you how to prepare and infuse EMPAVELI before you use it for the first time.
- Use EMPAVELI exactly as your healthcare professional tells you. Your healthcare professional will tell you how much EMPAVELI to infuse and how often to infuse EMPAVELI. Do not infuse more or less than your healthcare professional tells you to.
- EMPAVELI is given by infusion under the skin (subcutaneously) into your stomach (abdomen), back of upper arms, hips, or thighs using an infusion pump.
- Remove a single carton from the refrigerator. Keep the vial in the carton at room temperature and allow it to warm up for about 30 minutes.
- Start the infusion right away after drawing EMPAVELI into the syringe.
- EMPAVELI infusion takes about 30 minutes to complete (if using 2 infusion sites) or about 60 minutes (if using 1 infusion site).

Usual dose:

- 1080 mg EMPAVELI 2 times a week by subcutaneous infusion.
- Do NOT change your dose or dosing interval without consulting your healthcare professional. If there is an increase in your LDH levels (enzyme in your blood), your healthcare professional may tell you to take EMPAVELI every 3 days (e.g. Day 1, Day 4, Day 7, Day 10, Day 13, and so forth).

Patients switching treatment to EMPAVELI from C5 inhibitor PNH medicine

- **If you are switching treatment to EMPAVELI from C5 inhibitor PNH medicine (i.e. eculizumab or ravulizumab):**
 - First 4 weeks, take both EMPAVELI and your C5 inhibitor treatment:
 - 1080 mg EMPAVELI 2 times a week (on Day 1 and 4 of each treatment week)
 - Current dose of C5 inhibitor medicine, as prescribed.
 - After 4 weeks, stop taking your C5 inhibitor medicine. Continue taking 1080 mg EMPAVELI 2 times a week.

Stopping EMPAVELI treatment

- Your healthcare professional will tell you how long you need to take this medicine. If you wish to stop using EMPAVELI, you must speak to your healthcare professional first. Stopping EMPAVELI suddenly can have serious effects.
- If your healthcare professional decides to stop your treatment with this medicine, follow their instructions for how to stop.
- **Stopping treatment with EMPAVELI may cause a breakdown of red blood cells due to PNH.** Your healthcare professional will closely monitor you for at least 8 weeks after stopping treatment for any signs of the destruction of red blood cells (hemolysis) due to PNH. Symptoms or problems that can happen due to red blood cell breakdown include:

○ decreased hemoglobin level in your blood/red blood cell count	○ tiredness
○ blood clots (thrombosis)	○ shortness of breath
	○ trouble swallowing

- blood in your urine
- pain in the stomach (abdomen)
- erectile dysfunction (ED) in males

If you have any of these signs and symptoms, contact your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much EMPAVELI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of EMPAVELI, take the missed dose as soon as possible. Take your next dose at your regularly scheduled time.

What are possible side effects from using EMPAVELI?

These are not all the possible side effects you may have when taking EMPAVELI. If you experience any side effects not listed here, tell your healthcare professional.

- injection site reactions (such as redness, swelling or hardening of skin)
- diarrhea
- injection site itching
- headache

Abnormal blood test results have been observed in patients taking EMPAVELI. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Fever		x	
Hemolysis (Breakdown of red blood cells): low blood counts (anemia), tiredness, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots		x	
Hypersensitivity (allergic reaction): shortness of breath, difficulty breathing, chest pain, swelling of face/tongue/throat, feeling dizzy/faint, itching of skin, rash.			x
RARE			
Hypertension (high blood pressure): You may not experience any symptoms, but possible symptoms associated with high blood pressure are: headache, blurred vision, fatigue, irregular, fast, hard heartbeats		x	
Paralysis of face		x	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		x	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store vials of EMPAVELI in the refrigerator (2°C to 8°C) in the original carton to protect from light.
- Do not use EMPAVELI past the expiration date stamped on the carton.
- Keep EMPAVELI out of reach and sight of children.

If you want more information about EMPAVELI:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.sobi.ca, or by calling 1-833-697-0049.

This leaflet was prepared by:

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

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Last Revised NOV 28, 2022

INSTRUCTIONS FOR USE

PrEMPAVELI™ (pegcetacoplan injection)

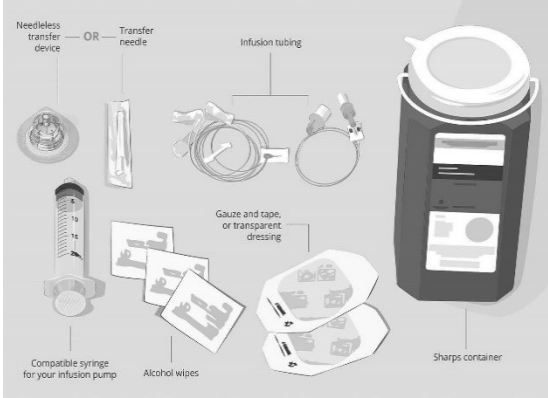
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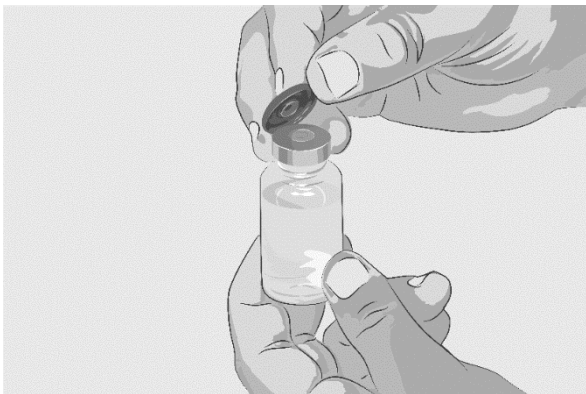
PLEASE READ THESE INSTRUCTIONS BEFORE USE

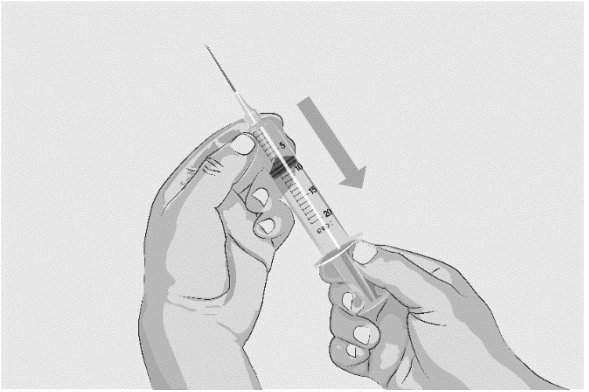
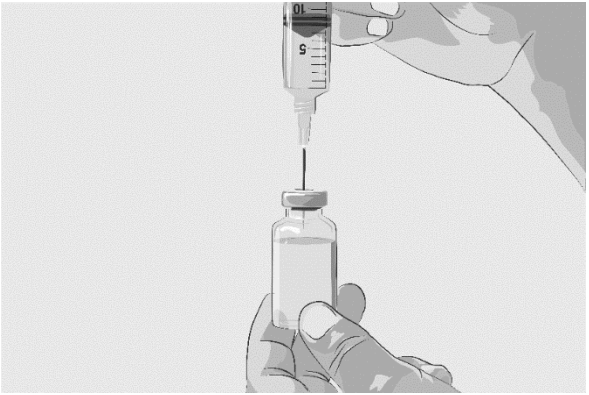

Read this Instructions for Use before you start using EMPAVELI and each time you get a refill. There may be new information. This information guide does not take the place of talking to your healthcare professional about your medical condition or treatment. Your healthcare professional will show you or your caregiver how to infuse EMPAVELI the right way before you use it for the first time. Please also read the Patient Medication Information insert carefully and ask your healthcare professional about any instructions you do not understand.

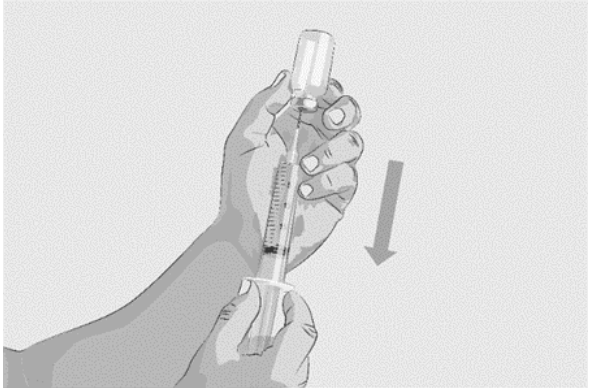
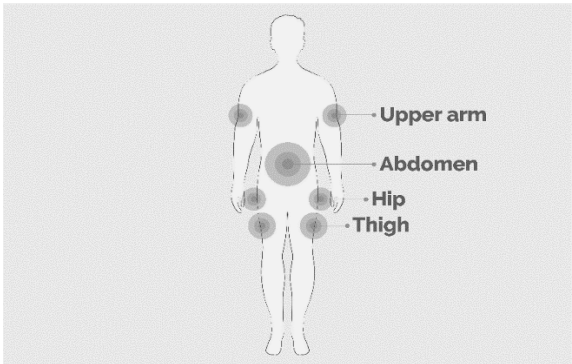
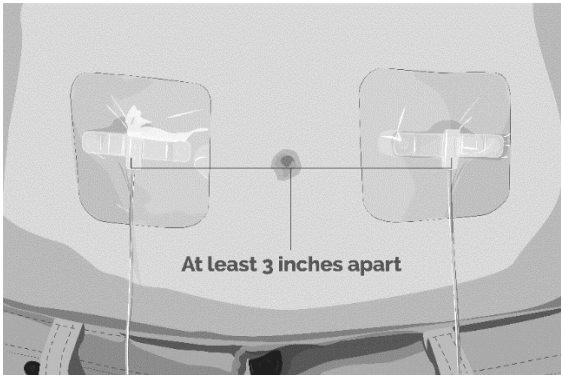
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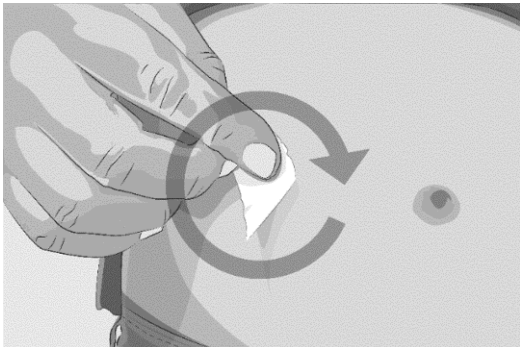
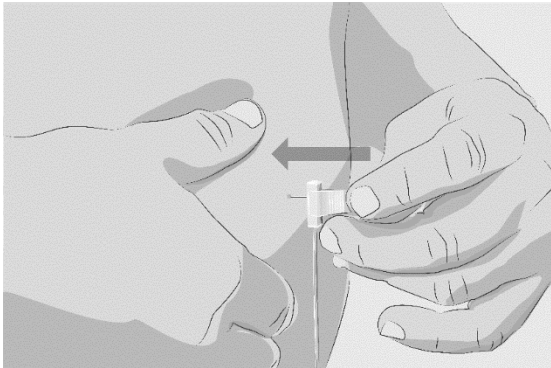
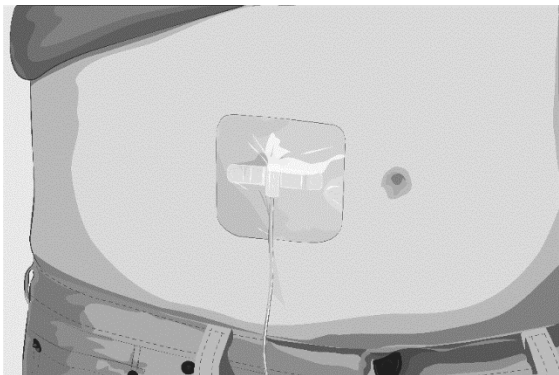
- Store vials of EMPAVELI in the refrigerator (2°C to 8°C) in the original carton to protect from light.
- Do not use EMPAVELI past the expiration date stamped on the carton.
- Keep EMPAVELI out of the reach and sight of children.


Step 1	Prepare for infusion Before you start: <ul style="list-style-type: none">• Find a well-lit, flat work surface, like a table.• Remove a single vial carton from the refrigerator. Keep the vial in the carton at room temperature and allow it to warm up for about 30 minutes.• Do NOT try to speed up the warming process. Gather your supplies (See Figure A): <ul style="list-style-type: none">• Infusion pump and manufacturer's instructions (not shown)• Compatible syringe for your infusion pump• Transfer needle OR needleless transfer device to draw up the medicine from the vial• Infusion set (not shown; varies according to device manufacturer's instructions)• Infusion tubing• Sharps container	Figure A: Supplies 
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	<ul style="list-style-type: none"> Alcohol wipes Gauze and tape, or transparent dressing 	
	Clean your work surface well using an alcohol wipe.	
	Wash your hands well with soap and water. Dry your hands.	
Step 2	<p>Check the vial and liquid</p> <p>Remove the vial from the carton. Carefully look at the liquid in the vial.</p> <p>EMPAVELI is a clear, colourless to slightly yellowish liquid. Check for particles or colour changes (See Figure B).</p> <p>Do NOT use the vial if:</p> <ul style="list-style-type: none"> The liquid looks cloudy, contains particles, or is dark yellow. The protective flip cap is missing or damaged. The expiration date on the label has passed. 	<p>Figure B</p> 
Step 3	<p>Prepare and fill syringe</p> <ul style="list-style-type: none"> Remove the protective flip cap from the vial to show the middle part of the gray rubber stopper of the EMPAVELI vial (See Figure C). Throw away the cap. Clean the stopper with a new alcohol wipe and allow the stopper to dry. <p>Option 1: If using a needleless transfer device (such as a vial adapter), follow the instructions provided by the device manufacturer.</p> <p>OR</p> <p>Option 2: If transfer is done using a transfer needle and a syringe, follow the instructions below:</p> <ul style="list-style-type: none"> Attach a sterile transfer needle to a sterile syringe. 	<p>Figure C</p> 

	<ul style="list-style-type: none"> • Pull back the plunger to the 20-mL mark to fill the syringe with air (See Figure D). • Make sure the vial is in upright position. Do NOT turn the vial upside down. Push the air-filled syringe with transfer needle attached through the center of the vial stopper. • The tip of the transfer needle should not be in the solution to avoid creating bubbles (See Figure E). • Gently push the air from the syringe into the vial. This will inject the air from the syringe into the vial. The air injected into the vial will allow the medicine to be withdrawn more easily. • Turn the vial upside down and insert the needle in the solution (See Figure F). 	<p>Figure D</p>  <p>Figure E</p>  <p>Figure F</p> 
	<p>With the transfer needle tip in the solution, slowly pull the plunger to fill the syringe with all the EMPAVELI liquid (See Figure G).</p> <p>Remove the filled syringe and the transfer needle from the vial.</p>	

	<ul style="list-style-type: none"> • Do NOT recap the transfer needle. Unscrew the needle and throw it away in the sharps container. 	<p>Figure G</p> 
Step 4	<p>Prepare infusion pump and tubing</p> <ul style="list-style-type: none"> • Gather the infusion pump supplies and follow the device manufacturer's instructions to prepare the pump and tubing. 	
Step 5	<p>Prepare the infusion site(s)</p> <ul style="list-style-type: none"> • Select an area on your abdomen [except for the 5 centimetres (2 inches) area around the belly button], thighs, hips, or upper arms for the infusion(s) (See Figure H). <p>Avoid the following infusion areas:</p> <ul style="list-style-type: none"> ○ Do NOT infuse into areas where the skin is tender, bruised, red, or hard. ○ Avoid infusing into tattoos, scars, or stretch marks. <ul style="list-style-type: none"> • Use a different site(s) from the last time you infused EMPAVELI. If there are multiple infusion sites, they should be at least 7.5 centimetres (3 inches) apart. Change (rotate) infusion sites in between each infusion (See Figure I). 	<p>Figure H</p>  <p>Figure I</p> 

	<ul style="list-style-type: none"> • Clean the skin at each infusion site(s) with a new alcohol wipe, starting at the center of each infusion site and working outward in a circular motion (See Figure J). • Let the skin dry. 	<p>Figure J</p> 
Step 6	<p>Insert and secure the infusion needle(s)</p> <ul style="list-style-type: none"> • Pinch the skin between your thumb and forefinger around the infusion site (where you plan to insert the needle). • Insert the needle into the skin (See Figure K). Follow the device manufacturer's instructions on the angle of the needle. • Secure the needle(s) using gauze and tape or a transparent dressing placed over the infusion site(s) (See Figure L). 	<p>Figure K</p>  <p>Figure L</p> 

Step 7	Start infusion <ul style="list-style-type: none"> Follow the device manufacturer's instructions to start the infusion. Start the infusion right away after drawing EMPAVELI into the syringe. <p>EMPAVELI infusion takes about 30 minutes to complete (if using 2 infusion sites) or about 60 minutes (if using 1 infusion site).</p>	
Step 8	Complete infusion <ul style="list-style-type: none"> Follow the device manufacturer's instructions to complete the infusion. 	
Step 9	Record infusion <ul style="list-style-type: none"> Record your treatment as directed by your healthcare professional. 	
Step 10	Clean up <ul style="list-style-type: none"> After the infusion is complete, remove the dressing and slowly take out the needle(s). Cover the infusion site with a new dressing. Remove the infusion set from the pump and throw it away into the sharps container or puncture-resistant container for safe disposal (See Figure M). Throw away all used disposable supplies as well as any unused product and the empty vial as recommended by your healthcare professional. Clean and store the infusion pump according to the device manufacturer's instructions. When your sharps disposal container is almost full, dispose of it according to local requirements or as instructed by your healthcare professional. 	<p>Figure M</p>  <p>The illustration shows a hand holding a used infusion set (needle and tubing) and disposing of it into a black sharps container. The container is a rectangular box with a white label and a clear window showing the interior. A white cap is being placed over the top of the container.</p>

To Call your healthcare professional to talk about any questions you may have. For questions or concerns visit the manufacturer's website www.sobi.ca, or call 1-833-697-0049.

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