▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - EMPAVELI® (PEGCETACOPLAN), SOLUTION FOR INJECTION

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

Use of EMPAVELI may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B, which may become rapidly life-threatening or fatal if not recognised and treated early [see *section 4.4, Special Warnings and Precautions for Use*].

- **Vaccinate and/or revaccinate according to current national vaccination guidelines such as the Australian Immunisation Handbook; vaccines against encapsulated bacteria such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B, are recommended.**
- **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. Patients who initiate EMPAVELI less than 2 weeks after vaccination must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. *See section 4.4, Special Warnings and Precautions for Use* for additional guidance on the management of the risk of serious infection.**
- **Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.**

1 NAME OF THE MEDICINE

Pegcetacoplan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 1080 mg pegcetacoplan in a pH 5.0, 10 mM acetate buffer.

For the full list of excipients, see section 6.1. List of Excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to slightly yellowish aqueous solution, practically free from visible particles, to be administered by subcutaneous infusion.

EMPAVELI solution for injection does not contain any antimicrobial preservatives. The vial is for single use in one patient on one occasion only. Discard any residue.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended Vaccination and Prophylaxis
Before receiving treatment with EMPAVELI

- *Patients with known history of vaccination*: Ensure that patients have received vaccines against encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B (Hib) within 2 years prior to starting EMPAVELI (see *section 4.4 Special Warnings and Precautions for Use*).
- *Patients without known history of vaccination*: Administer required vaccines at least 2 weeks prior to receiving the first dose of EMPAVELI (see *section 4.4 Special Warnings and Precautions for Use*).
    - If immediate therapy with EMPAVELI is indicated, administer required vaccines as soon as possible and provide patients with antibacterial drug prophylaxis until 2 weeks after vaccination (see *section 4.4 Special Warnings and Precautions for Use*).

Dosage
Adult Patients with PNH
EMPAVELI is administered twice weekly as a 1,080 mg subcutaneous infusion with a commercially available syringe system infusion pump that can deliver doses up to 20 mL. (*See Method of administration* and *Instructions for Use*.) 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.

PNH is a chronic disease and treatment with EMPAVELI is recommended to continue for the patient's lifetime, unless the discontinuation of EMPAVELI is clinically indicated (see *section 4.4 Special Warnings and Precautions for Use*).

Patients switching to EMPAVELI from a C5 inhibitor (eculizumab rmc, ravulizumab rch)
For the first 4 weeks, EMPAVELI is administered as twice weekly subcutaneous doses of 1,080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimise the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient should discontinue treatment with the C5 inhibitor before continuing on monotherapy with EMPAVELI.

Dose adjustment for EMPAVELI
The dosing regimen may be changed to 1,080 mg every third day if a subject has a lactate dehydrogenase (LDH) level greater than 2 × upper limit of normal (ULN).

In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.

Missed dose of EMPAVELI
If a dose of EMPAVELI is missed, and the next scheduled dose has not been administered, then the missed dose should be administered as soon as possible, and then the regular schedule resumed.

Two doses should not be administered on the same day; however, it is acceptable to administer doses on 2 consecutive days.

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

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

Infuse EMPAVELI in the abdomen, thighs, hips, or upper arms. Infusion sites should be at least 7.5 cm apart from each other. Rotate infusion sites between administration. Do not infuse into areas 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.

Renal impairment
Renal impairment had no effect on the pharmacokinetics of pegcetacoplan; therefore, dose adjustment of EMPAVELI in patients with renal impairment is not necessary (see *section 5.2 Pharmacokinetic Properties*).

Hepatic impairment
The safety and efficacy of EMPAVELI have not been studied in patients with hepatic impairment; however, population pharmacokinetic data suggest that no dose adjustment is required in patients with hepatic impairment (see *section 5.2 Pharmacokinetic Properties*).

4.3 CONTRAINDICATIONS

EMPAVELI is contraindicated in patients with:
- Hypersensitivity to pegcetacoplan or to any of the excipients.
- Unresolved infection caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* (see section 4.4).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious Infections Caused by Encapsulated Bacteria
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. 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 serious infection, 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.

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

Monitoring PNH Manifestations after Discontinuation of EMPAVELI
If patients with PNH discontinue treatment with EMPAVELI, they should be closely monitored for signs and symptoms of serious intravascular haemolysis. Intravascular haemolysis is identified by elevated LDH levels along with sudden decrease in PNH clone size or haemoglobin, or reappearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), major adverse vascular event (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. In addition, slow weaning should be considered, and patients should be closely monitored for at least 8 weeks to detect haemolysis and other reactions, as alternative complement inhibitors may not prevent haemolysis as efficiently.

PNH laboratory monitoring
Patients with PNH receiving EMPAVELI should be monitored regularly for signs and symptoms of haemolysis, including measuring LDH levels, and may require dose adjustment within the recommended dosing schedule (see section 4.2).

Excipients with known effect
This medicinal product contains sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into consideration for patients known or suspected to have the rare genetic disorder of hereditary fructose intolerance (HFI).

Use in the elderly
Although there were no apparent age-related differences observed in clinical studies, the number of patients aged 65 years and over was not sufficient to determine whether they respond differently from younger subjects.

Paediatric use
The safety and efficacy of pegcetacoplan in children with PNH from birth to less than 18 years have not been established.

Effects on 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, the use of silica reagents in coagulation panels should be avoided.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical interaction studies have been performed. Nonclinical studies showed that pegcetacoplan has a low potential for pharmacokinetic drug interactions, as it did not induce or inhibit cytochrome P450 isozyme activities or serve as a substrate and/or inhibitor for human drug transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 dosed daily subcutaneously for up to 9 months at exposure levels up to 6 times the clinical AUC.

Use in pregnancy – Category B3
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.

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. Pregnancy testing is advised for females of reproductive potential prior to treatment with EMPAVELI.

Use of EMPAVELI in pregnancy should be carefully considered, with regard to the specific risks of PNH (including maternal and neonatal death and non-live birth) and benefits for each patient. EMPAVELI should be used during pregnancy only if the potential benefit justifies the potential risk to the mother, fetus, and/or neonate.

Clinical Considerations
Disease-associated maternal and/or fetal/neonatal risk
In pregnancy, PNH 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.

Animal Data
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. The relative exposure at the no-adverse-effect level for this effect (7 mg/kg/day) was similar to that anticipated clinically (1.3 times AUC). 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. Minimal systemic exposure to pegcetacoplan (less than 1% of maternal exposure) was detected in fetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester.

Use in lactation
It is not known whether pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data and the chemical nature of pegcetacoplan suggest that the risk of clinically relevant exposure to the infant is minimal (see below).

Minimal (less than 1%) pegcetacoplan excretion in milk has been demonstrated in monkeys; therefore, the probability of clinically relevant exposure of breastfed infant through breastmilk is considered low.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience in Adult Patients with PNH

The data described below in Table 1 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 in Study APL2-302.

Serious adverse events were reported in 7 (17%) patients with PNH receiving EMPAVELI. The most common serious adverse reaction in patients treated with EMPAVELI was infections (5%).

Table 1: Adverse Events Reported in ≥5% of Patients Treated with EMPAVELI

Body System **Adverse Event**	**EMPAVELI** **(N=41)** **n (%)**	**Eculizumab** **(N=39)** **n (%)**
General disorders and administration site conditions		
Injection site erythema	7 (17.1)	0
Injection site reaction	5 (12.2)	0
Injection site swelling	4 (9.8)	0
Injection site induration	3 (7.3)	0
Asthenia	3 (7.3)	3 (7.7)
Gastrointestinal disorders		
Diarrhoea	9 (22.0)	1 (2.6)
Abdominal pain	5 (12.2)	4 (10.3)
Blood and lymphatic system disorders		
Haemolysis	4 (9.8)	9 (23.1)
Musculoskeletal and connective tissue disorders		
Back pain	3 (7.3)	4 (10.3)
Pain in extremity	3 (7.3)	1 (2.6)
Nervous system disorders		
Headache	3 (7.3)	9 (23.1)
Vascular disorders		
Hypertension	3 (7.3)	1 (2.6)

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

- Intestinal ischemia
- Biliary sepsis
- Hypersensitivity pneumonitis

The data described in Table 2 reflect the exposure in the 80 adult patients in Study APL2-302 who received EMPAVELI at the recommended dosing regimens for up to 48 weeks.

Table 2: Adverse Events Reported in ≥5% of Patients Treated with EMPAVELI for up to 48 Weeks

MedDRA SOC	**Very common** **≥1/10**	**Common** **≥1/100 to <1/10**
Infections and infestations	Nasopharyngitis	Urinary tract infection Oral herpes

	Upper respiratory tract infection	Gastroenteritis Sinusitis
Blood and lymphatic system disorders	Haemolysis	Thrombocytopenia
Psychiatric disorders		Anxiety
Nervous system disorders	Headache	
Vascular disorders		Hypertension
Respiratory, thoracic and mediastinal disorders	Cough	Oropharyngeal pain Epistaxis
Gastrointestinal disorders	Diarrhoea Abdominal pain	Abdominal distension
Skin and subcutaneous tissue disorders		Erythema
Musculoskeletal and connective tissue disorders	Arthralgia	Pain in extremity Back pain Myalgia
Renal and urinary disorders		Acute kidney injury
General disorders and administration site conditions	Injection site erythema Fatigue Pyrexia	Injection site pruritus Asthenia Injection site bruising Injection site induration Injection site reaction Injection site swelling Injection site pain
Injury, poisoning and procedural complications		Contusion Vaccination complication

Description of selected adverse reactions

Injection site reactions

Injections site reactions (e.g., erythema, swelling, induration, pruritus, and pain) have been reported during Study APL2-302. These reactions were not severe and did not lead to discontinuation of treatment.

Diarrhoea

Cases of diarrhoea have been reported during Study APL2-302, none of them were severe or led to discontinuation of treatment.

Haemolysis

Haemolysis and haemolytic anemia have been reported during Study APL2-302 but occurred less frequently in the EMPAVELI group than in the eculizumab group during the randomised controlled period (RCP) (Week 16).

Immunogenicity

The immunogenicity of EMPAVELI has been evaluated using specific anti-drug antibody (ADA) assays, one specific for the detection of ADAs against the peptide moiety of pegcetacoplan (anti-pegcetacoplan peptide) and a second one specific for ADAs against the polyethylene glycol (PEG) component of pegcetacoplan (anti-PEG).

Anti-drug antibody incidence (seroconverted ADA or boosted ADA from pre-existing level) was low, and when present, had no noticeable impact on the pharmacokinetics/pharmacodynamics (PK/PD), efficacy, or safety profile of pegcetacoplan. Throughout Study APL2-302, up to Week 48, 2 out of 80 patients developed anti-pegcetacoplan peptide antibodies. Six out of 80 patients developed anti-PEG antibody incidence; two were seroconversion and four were treatment-boosted.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reportingproblems.

4.9 OVERDOSE

No case of overdose has been reported during clinical studies.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: LO4AAXX

Mechanism of action
Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, extravascular haemolysis (EVH) is facilitated by C3b opsonization while intravascular haemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b and MAC formation, thereby controlling the mechanisms that lead to EVH and IVH. These functions of pegcetacoplan underlie the observed sustained reduction in complement-mediated haemolytic activity in patients with PNH.

Pharmacodynamic effects
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. The baseline percentage of PNH Type II + III RBCs was 66.80%, which then increased to 93.85% at Week 16. The mean percentage of PNH Type II + III RBCs with C3 deposition was 17.73% at baseline and this decreased to 0.20% at Week 16. Pegcetacoplan treatment of patients with PNH resulted in the improvement of haemoglobin (Hb) level and reduction of absolute reticulocyte count (ARC) and LDH (see *Clinical trials*).

Clinical trials

Paroxysmal Nocturnal Haemoglobinuria (PNH)

The efficacy and safety of EMPAVELI in patients with PNH was assessed in an open-label, randomised, active comparator controlled 16-week Phase 3 study (Study APL2-302; NCT03500549). This 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.

The dose of EMPAVELI was 1,080 mg twice weekly. 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 randomised 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 RCP. If required, the dose of EMPAVELI could be adjusted to 1,080 mg every 3 days. Randomisation 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/mm^3; ≥100,000/mm^3). Following completion of the RCP, all patients entered a 32-week open-label period and received monotherapy with EMPAVELI. All patients who completed the 48-week period were eligible to enroll in a separate long-term extension study.

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 who are receiving treatment with a complement inhibitor. EMPAVELI was administered as a subcutaneous infusion; the infusion time was approximately 20 to 40 minutes.

The primary efficacy endpoint was change from baseline to Week 16 (during RCP) in haemoglobin 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.

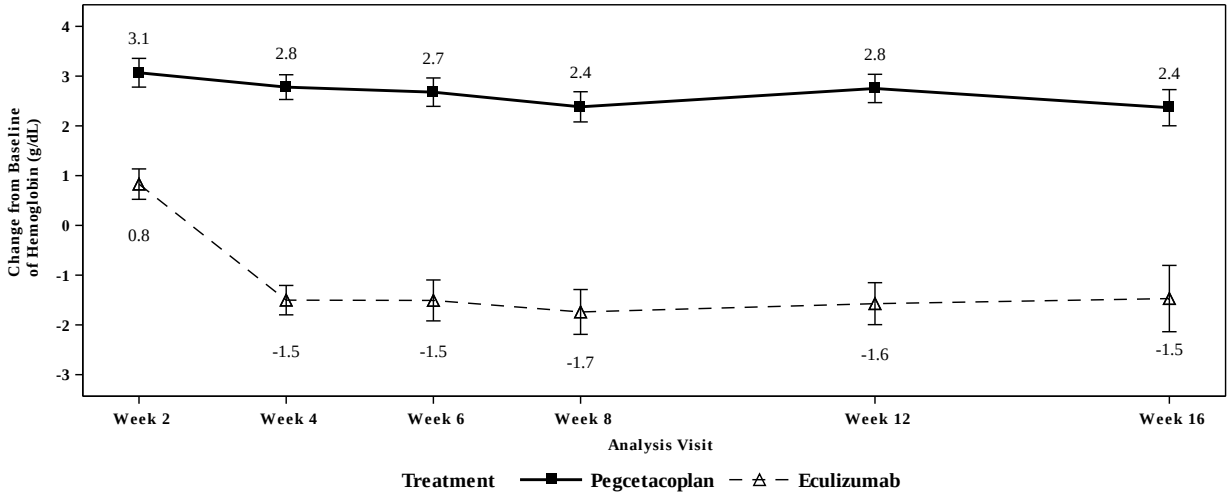
A total of 80 patients were randomised to receive treatment, 41 to EMPAVELI and 39 to eculizumab. Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 3). A total of 38 patients in the group treated with EMPAVELI and 39 patients in the eculizumab group completed the 16-week RCP and continued into the 32-week open-label period. Because of adverse events of haemolysis, 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)
Dose level of eculizumab at baseline			
Every 2 weeks IV 900 mg	n (%)	26 (63.4)	30 (76.9)
Every 11 days IV 900 mg	n (%)	1 (2.4)	0
Every 2 weeks IV 1200 mg	n (%)	12 (29.3)	9 (23.1)
Every 2 weeks IV 1500 mg	n (%)	2 (4.9)	0
Female	n (%)	27 (65.9)	22 (56.4)
Time since diagnosis of PNH (years) to Day -28	Mean (SD)	8.7 (7.4)	11.7 (9.6)
Haemoglobin level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
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 (count/mm^3)	Mean (SD)	167 (98.3)	147 (68.8)
<100,000	n (%)	12 (29.3)	9 (23.1)
≥100,000	n (%)	29 (70.7)	30 (76.9)

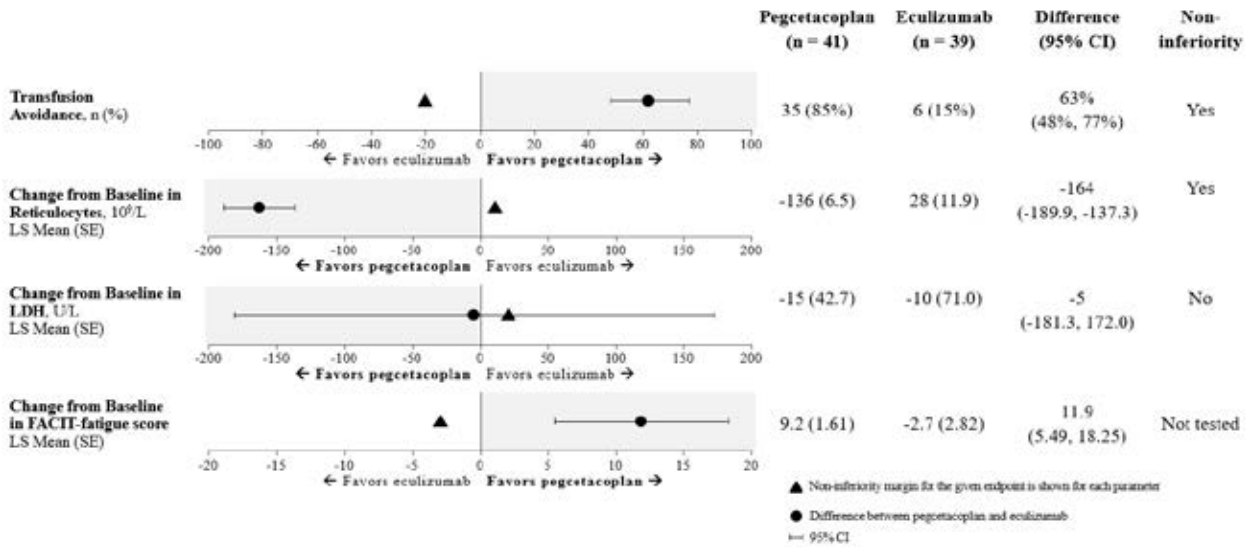
EMPAVELI was superior to eculizumab for the primary endpoint of the haemoglobin change from baseline (P<0.0001). The adjusted mean change from baseline in Hb level was 2.4 g/dL in the group treated with EMPAVELI versus -1.5 g/dL in the eculizumab group, demonstrating an adjusted mean increase of 3.8 g/dL with EMPAVELI compared to eculizumab at Week 16 (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 (± SE) Change from Baseline to Week 16 in Haemoglobin (g/dL)



The adjusted means, treatment difference, confidence intervals, and statistical analyses performed for the key secondary endpoints are shown in Figure 2.

Figure 2. Key Secondary Endpoints Analysis



In patients treated with EMPAVELI, primary and key secondary efficacy analyses showed no notable differences based on sex, race, or age.

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption
EMPAVELI is administered subcutaneously and is gradually absorbed into the systemic circulation with a median T_{max} between 108 and 144 hours (4.5 to 6.0 days). Steady-state serum concentrations following twice weekly dosing at 1,080 mg in PNH patients were achieved approximately 4 to 6 weeks following the first dose and mean (%CV) steady-state serum concentrations ranged between 655 mcg/mL (18.6%) to 706 mcg/mL (15.1%) in patients treated for 16 weeks.

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

Metabolism/Excretion
Based on its PEGylated peptide structure, the metabolism of pegcetacoplan is expected to occur via catabolic pathways and be degraded into small peptides and amino acids. Results of a radiolabeled study in cynomolgus monkeys suggest the primary route of elimination is via urinary 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.

Linearity/Non-linearity
Exposure of pegcetacoplan increases in a dose-proportional manner from 45 to 1440 mg.

Special Populations
No impact on the pharmacokinetics of pegcetacoplan was identified with age, sex, race, and hepatic function based on the results of population PK analysis.

Elderly Population
Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 years and over was not sufficient to determine whether they respond differently from younger patients.

Renal Insufficiency
In a study of 8 patients with severe renal impairment, defined as creatine clearance (CrCl) less than 30 mL/min (with 4 patients with values less than 20 mL/min), renal impairment had no effect on the pharmacokinetics of pegcetacoplan (see *section 4.2 Dose and Method of Administration*).

5.3 PRECLINICAL SAFETY DATA

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sorbitol
Glacial acetic acid
Sodium acetate trihydrate
Sodium Hydroxide
Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C – 8°C in a refrigerator. Do not freeze.
Keep EMPAVELI in its original package to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Sterile solution present in a vial (Type I glass) with a stopper (cholorobutyl), and a seal (aluminium) with a flip-off cap (polypropylene).

Each 20 mL vial contains 1.3 mL overfill.

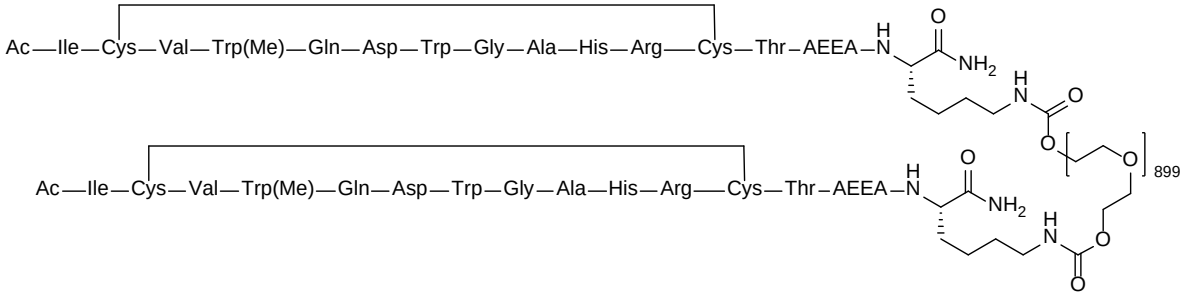
Pack sizes of 1 or 8 vials. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Pegcetacoplan, the active ingredient in EMPAVELI solution for subcutaneous infusion 1,080 mg/20 mL, is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to both ends of a linear polyethylene glycol (PEG) molecule. The molecular weight of pegcetacoplan is approximately 43.5 kiloDaltons (kDa). The peptide moieties bind to complement C3 and exert a broad inhibition of the complement cascade. The 40-kDa PEG moiety imparts improved solubility and longer residence time in the body after administration of the drug product. The structure of pegcetacoplan is shown below.



The chemical name is poly(oxy-1,2-ethanediyl), α-hydro, ω-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-α-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N^6-carboxy-L-lysinamide cyclic (2→12)-(disulfide).

The chemical formula is $C_{170}H_{248}N_{50}O_{47}S_4 \cdot (C_2H_4O)_n$ n = 800-1100.

CAS registry number: 2019171-69-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Swedish Orphan Biovitrum Pty Ltd
Floor 22, 44 Market Street
Sydney NSW 2000

https://au.sobi.com

Medical enquiries: 1800 570 605.

9 DATE OF FIRST APPROVAL

3 February 2022

10 DATE OF REVISION

28 March 2022

Summary table of changes

Section changed	Summary of new information
8	Update to sponsor details
2	Revised composition representation and reference to sorbitol deleted
3	Revised description of the product
6.1	Added sodium hydroxide
6.5	Reference to “54 mg/mL” has been deleted
9	Date of first approval changed to 3 February 2022