ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI 1 080 mg solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 1 080 mg of pegcetacoplan.
Each mL contains 54 mg of pegcetacoplan.

Excipients with known effect
Each mL contains 41 mg of sorbitol.
Each vial contains 820 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless to slightly yellowish aqueous solution with pH 5.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ASPAVELI is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

4.2 Posology and method of administration

Therapy should be initiated under the supervision of a healthcare professional experienced in the management of patients with haematological disorders. Self-administration and home infusion should be considered for patients who have tolerated treatment well in experienced treatment centres. The decision of a possibility of self-administration and home infusions should be made after evaluation and recommendation from the treating physician.

Posology

Pegcetacoplan can be given by a healthcare professional or administered by the patient or caregiver following proper instruction.

Pegcetacoplan is administered twice weekly as a 1 080 mg subcutaneous infusion with a commercially available syringe system infusion pump or on-body delivery system, 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.

PNH is a chronic disease and treatment with ASPAVELI is recommended to continue for the patient's lifetime, unless the discontinuation of this medicinal product is clinically indicated (see section 4.4).

Patients switching to ASPAVELI from a C5 inhibitor
For the first 4 weeks, pegcetacoplan 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 C5 inhibitor before continuing on monotherapy with ASPAVELI.

Switches from complement inhibitors other than eculizumab have not been studied. Discontinuing other complement inhibitors before reaching steady-state of pegcetacoplan should be done with caution (see section 5.2).

Dose adjustment
The dosing regimen may be changed to 1 080 mg every third day (e.g., Day 1, Day 4, Day 7, Day 10, Day 13, and so forth) if a patient has a lactate dehydrogenase (LDH) level greater than 2 x upper limit of normal (ULN). In the event of a dose increase, LDH should be monitored twice weekly for at least 4 weeks (see section 4.4).

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

Special populations

Elderly
Although there were no apparent age-related differences observed in clinical studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients. There is no evidence indicating any special precautions are required for treating an elderly population.

Renal impairment
Severe renal impairment (creatinine clearance <30 mL/min) had no effect on the pharmacokinetics (PK) of pegcetacoplan; therefore, pegcetacoplan dose adjustment in patients with renal impairment is not necessary. There are no data available for the use of pegcetacoplan in patients with end-stage renal disease (ESRD) requiring haemodialysis (see section 5.2).

Hepatic impairment
The safety and efficacy of pegcetacoplan have not been studied in patients with hepatic impairment; however, no dose adjustment is recommended, as hepatic impairment is not expected to impact clearance of pegcetacoplan.

Paediatric population
The safety and efficacy of ASPAVELI in children with PNH aged 0 to <18 years have not yet been established. No data are available.

This medicinal product should not be used in children <12 years of age, as non-clinical safety data are not available for this age group.

Method of administration

ASPAVELI should only be administered via subcutaneous administration using a commercially available syringe system infusion pump or on-body delivery system.

This medicinal product can be self-administered. When self-administration is initiated, the patient will be instructed by a qualified healthcare professional in infusion techniques, the use of a syringe system infusion pump or an on-body delivery system, the keeping of a treatment record, the recognition of possible adverse reactions, and measures to be taken in case these occur.

- When using a syringe system infusion pump, ASPAVELI should be infused in the abdomen, thighs, hips, or upper arms. Infusion sites should be at least 7.5 cm apart from each other. The infusion sites should be rotated between administrations. The infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site).

- When using an on-body delivery system, ASPAVELI should be infused at a site on the abdomen. The infusion site should be rotated between administrations following the device manufacturer´s instructions. The infusion time varies by patient and typically ranges from 30 to 60 minutes.

Infusion into areas where the skin is tender, bruised, red, or hard should be avoided. Infusion into tattoos, scars, or stretch marks should be avoided. The infusion should be started promptly after drawing this medicinal product into the syringe. Administration should be completed within 2 hours after preparing the syringe. For instructions on the preparation and infusion of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to pegcetacoplan or to any of the excipients listed in section 6.1.

Pegcetacoplan therapy must not be initiated in patients:
- with unresolved infection caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae* (see section 4.4).
- who are not currently vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see section 4.4).

4.4 Special warnings and precautions for use

Serious infections caused by encapsulated bacteria
The use of pegcetacoplan may predispose individuals to serious infections caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae*. To reduce the risk of infection, all patients must be vaccinated against these bacteria according to applicable local guidelines at least 2 weeks prior to receiving pegcetacoplan, unless the risk of delaying therapy outweighs the risk of developing an infection.

Patients with known history of vaccination
Before receiving treatment with pegcetacoplan, in patients with a known history of vaccination, it should be ensured 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 within 2 years prior to starting pegcetacoplan.

Patients without known history of vaccination
For patients without known history of vaccination, the required vaccines should be administered at least 2 weeks prior to receiving the first dose of pegcetacoplan. If immediate therapy is indicated, the required vaccines should be administered as soon as possible and the patient treated with appropriate antibiotics until 2 weeks after vaccination.

Monitoring patients for serious infections
Vaccination may not be sufficient to prevent serious infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. All patients should be monitored for early signs of infections caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae*, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. Patients should be informed of these signs and symptoms, and steps taken to seek medical care immediately. Physicians must discuss the benefits and risks of pegcetacoplan therapy with patients.

Hypersensitivity
Hypersensitivity reactions have been reported. If a severe hypersensitivity reaction (including anaphylaxis) occurs, infusion with pegcetacoplan must be discontinued immediately, and appropriate treatment instituted.

Injection site reactions
Injection site reactions have been reported with the use of subcutaneous pegcetacoplan (see section 4.8). Patients should be trained appropriately in proper injection technique.

PNH laboratory monitoring
Patients with PNH receiving pegcetacoplan 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).

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.

Treatment discontinuation for PNH
If patients with PNH discontinue treatment with pegcetacoplan, they should be closely monitored for signs and symptoms of serious intravascular haemolysis. Serious 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, dyspnoea, major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. If discontinuation of this medicinal product is necessary, alternate therapy should be considered. If serious haemolysis occurs after discontinuation, consider the following procedures/treatments: blood transfusion (packed RBCs), exchange transfusion, anticoagulation, and corticosteroids. Patients should be closely monitored for at least 8 weeks from the last dose, representing more than 5 half-lives of this medicinal product, to allow for medicinal product washout (see section 5.2) to detect serious haemolysis and other reactions. In addition, slow weaning should be considered.

Contraception in women of childbearing 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 section 4.6).

Polyethylene glycol (PEG) accumulation
ASPAVELI 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 section 5.3). Regular laboratory testing of renal function is recommended.

Educational materials
All physicians who intend to prescribe ASPAVELI must ensure they have received and are familiar with the physician educational material. Physicians must explain and discuss the benefits and risks of ASPAVELI therapy with the patient and provide them with the patient information pack and the patient card. The patient should be instructed to seek prompt medical care if they experience any sign or symptom of serious infection or hypersensitivity during therapy with ASPAVELI, especially if indicative of infection with encapsulated bacteria.

Excipients with known effect
Sorbitol content
ASPAVELI 1 080 mg contains 820 mg sorbitol in each vial.

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

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say, essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Women of childbearing 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. For women planning to become pregnant, the use of pegcetacoplan may be considered following an assessment of the risks and benefits (see Pregnancy).

Pregnancy
There are no or limited amount of data from the use of pegcetacoplan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Pegcetacoplan is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether pegcetacoplan is excreted in human milk. The potential for absorption and harm to the breastfed infant is unknown. Animal data suggest a low excretion (less than 1%, not pharmacologically significant) of pegcetacoplan in monkey milk (see section 5.3). It is unlikely that a breastfed infant would have clinically relevant exposure.

It is recommended to discontinue breast-feeding during pegcetacoplan treatment.

Fertility
No animal or human data on the effect of pegcetacoplan on fertility are available. In toxicity studies, there were no microscopic abnormalities in male or female reproductive organs in monkeys (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions in patients treated with pegcetacoplan were injection site reactions: injection site erythema, injection site pruritus, injection site swelling, injection site pain, injection site bruising. Other adverse reactions reported in more than 10% of patients during clinical studies were upper respiratory tract infection, diarrhoea, haemolysis, abdominal pain, headache, fatigue, pyrexia, cough, urinary tract infection, vaccination complication, pain in extremity, dizziness, arthralgia and back pain. The most commonly reported serious adverse reactions were haemolysis and sepsis.

Tabulated list of adverse reactions

Table 1 gives the adverse reactions observed from the clinical studies and postmarketing experience with pegcetacoplan in patients with PNH. Adverse reactions are listed by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100) or rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), and not known (cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions from clinical trials[1] and postmarketing experience

MedDRA System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection Urinary tract infection
	Common	Sepsis[2] COVID-19 Gastrointestinal infection Fungal infection Skin infection Oral infection Ear infection Infection Respiratory tract infection Viral infection Bacterial infection Vaginal infection Eye infection
	Uncommon	Cervicitis Groin infection Pneumonia Nasal abscess Tuberculosis Oesophageal candidiasis COVID-19 pneumonia Anal abscess
Blood and lymphatic system disorders	Very common	Haemolysis
	Common	Thrombocytopenia Neutropenia
Metabolism and nutrition disorders	Common	Hypokalaemia
Nervous system disorders	Very common	Headache Dizziness
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea Epistaxis Oropharyngeal pain Nasal congestion
Gastrointestinal disorders	Very common	Abdominal pain Diarrhoea
	Common	Nausea
Skin and subcutaneous tissue disorders	Common	Erythema Rash Urticaria[3]

MedDRA System Organ Class	Frequency	Adverse reaction
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Back pain Pain in extremity
	Common	Myalgia Muscle spasms
Renal and urinary disorders	Common	Acute kidney injury Chromaturia
General disorders and administration site conditions	Very common	Injection site erythema Injection site pruritus Injection site swelling Injection site bruising Fatigue Pyrexia Injection site pain
	Common	Injection site reaction Injection site induration
Investigations	Common	Alanine aminotransferase increased Bilirubin increased
Injury, poisoning and procedural complications	Very common	Vaccination complication[4]

[1]Studies APL2-308, APL2-302, APL2-202, APL2-CP-PNH-204, and APL-CP0514 in PNH patients. Medically similar terms are grouped, where appropriate, on the basis of similar medical concept.
[2]Sepsis includes one case of septic shock.
[3]Estimated from both clinical trial- and post marketing experience.
[4]Vaccination complications were related to the mandatory vaccinations.

Description of selected adverse reactions

Infections

Based on its mechanism of action, the use of pegcetacoplan may potentially increase the risk of infections, particularly infections caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* (see section 4.4). No serious infection caused by encapsulated bacteria was reported during Study APL2-302. Forty-eight patients experienced an infection during the study. The most frequent infections in patients treated with pegcetacoplan during Study APL2-302 were upper respiratory tract infection (28 cases, 35%). Most infections reported in patients treated with pegcetacoplan during study APL2-302 were non-serious, and predominantly mild in intensity. Ten patients developed infections reported as serious including one patient who died due to COVID-19. The most frequent serious infections were sepsis (3 cases) (leading to discontinuation of pegcetacoplan in one patient) and gastroenteritis (3 cases); all of which resolved. Eleven patients experienced an infection during study APL2-308. All but one infection were reported as mild or moderate in intensity. One patient who had an infection developed septic shock and died.

Haemolysis

Nineteen patients reported haemolysis during Study APL2-302 in patients treated with pegcetacoplan. Seven cases were reported as serious, and 5 cases led to discontinuation of pegcetacoplan and the dose of pegcetacoplan was increased in 10 patients. There were 3 cases of haemolysis during study APL2-308 in patients treated with pegcetacoplan. None of these cases were reported as serious or led to discontinuation of pegcetacoplan. The dose of pegcetacoplan was increased in all 3 patients.

Immunogenicity

Anti-drug antibody (ADA) incidence (seroconverted ADA or boosted ADA from pre-existing level) were low, and when present, had no noticeable impact on the PK/PD, efficacy, or safety profile of pegcetacoplan. Throughout studies APL2-302 and APL2-308, 3 out of 126 patients who were exposed to pegcetacoplan had confirmed positive anti-pegcetacoplan peptide antibodies. All 3 patients also tested positive for neutralising antibody (NAb). NAb response had no apparent impact on PK or

clinical efficacy. Eighteen out of 126 patients developed anti-PEG antibodies; 9 were seroconversions and 9 were treatment-boosted.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported to date. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Complement inhibitors, ATC code: L04AJ03

Mechanism of action
Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa PEG molecule. 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 medicinal product.

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 opsonisation 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.

Pharmacodynamic effects
In Study APL2-302, the mean C3 concentration increased from 0.94 g/L at baseline to 3.83 g/L at Week 16 in the pegcetacoplan group and sustained through Week 48. In Study APL2-308, the mean C3 concentration increased from 0.95 g/L at baseline to 3.56 g/L at Week 26.

In Study APL2-302, the mean percentage of PNH Type II + III RBCs increased from 66.80% at baseline, to 93.85% at Week 16 and sustained through Week 48. In Study APL2-308, the mean percentage of PNH Type II + III RBCs increased from 42.4% at baseline to 90.0% at Week 26.

In Study APL2-302, the mean percentage of PNH Type II + III RBCs with C3 deposition was decreased from 17.73% at baseline to 0.20% at Week 16 and sustained through Week 48. In Study APL2-308, the mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 2.85% at baseline to 0.09% at Week 26.

Clinical efficacy and safety
The efficacy and safety of pegcetacoplan in patients with PNH was assessed in two open-label, randomised-controlled phase 3 studies: in complement inhibitor-experienced patients in Study APL2-302 and in complement inhibitor-naïve patients in Study APL2-308. In both studies the dose of pegcetacoplan was 1 080 mg twice weekly. If required, the dose could be adjusted to 1 080 mg every 3 days.

Study in complement inhibitor-experienced adult patients (APL2-302)

Study APL2-302 was an open-label, randomised study with an active comparator-controlled period of 16 weeks followed by a 32-week open label period (OLP). 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 haemoglobin levels <10.5 g/dL. Eligible patients entered a 4-week run-in period during which they received pegcetacoplan 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 pegcetacoplan twice weekly or their current dose of eculizumab through the duration of the 16-week randomised controlled period (RCP). 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). Patients who completed the RCP entered the OLP during which all patients received pegcetacoplan for up to 32 weeks (patients who received eculizumab during the RCP entered a 4-week run-in period before switching to pegcetacoplan monotherapy).

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 haemoglobin level. Baseline was defined as the average of measurements prior to the first dose of pegcetacoplan (at the beginning of the run-in period). 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 entered the run-in period. At the end of the run-in period, all 80 were randomised, 41 to pegcetacoplan and 39 to eculizumab. Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 2). A total of 38 patients in the group treated with pegcetacoplan and 39 patients in the eculizumab group completed the 16-week RCP and continued into the 32-week open-label period. In total, 12 of 80 (15%) patients receiving pegcetacoplan discontinued due to adverse events. Per protocol 15 patients had their dose adjusted to 1 080 mg every 3 days. Twelve patients were evaluated for benefit and 8 of the 12 patients demonstrated benefit from the dose adjustment.

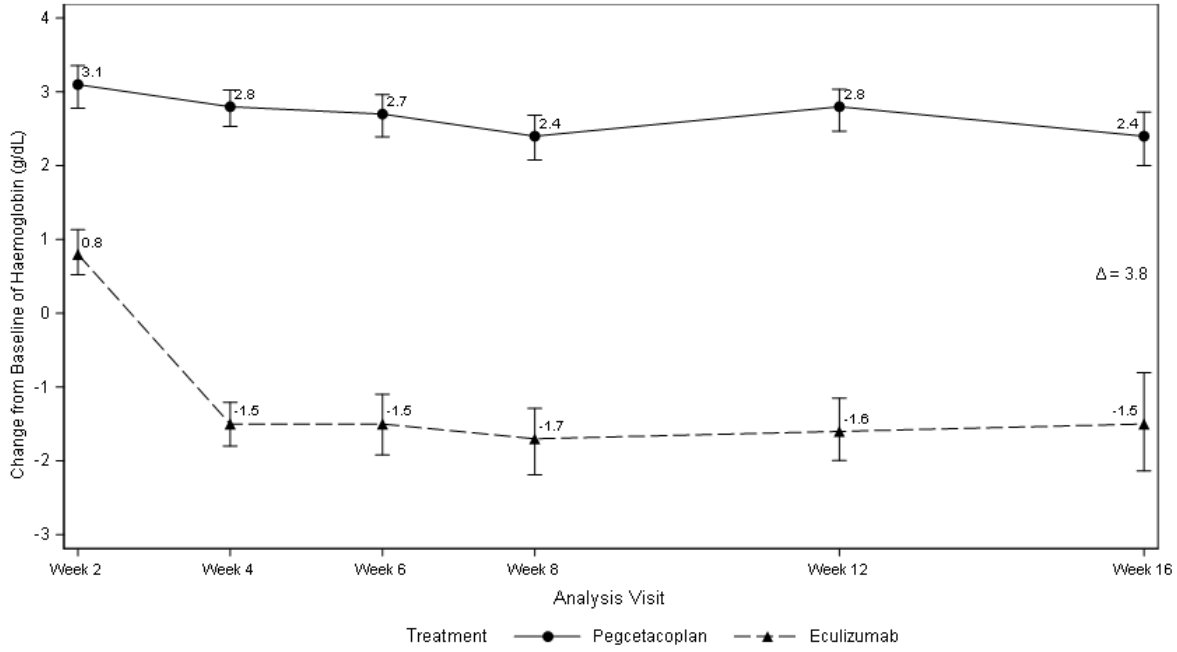
Table 2: Patient baseline demographics and characteristics in Study APL2-302

Parameter	Statistics	Pegcetacoplan (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)
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 1 200 mg	n (%)	12 (29.3)	9 (23.1)
Every 2 weeks IV 1 500 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)	11.4 (9.7)
Haemoglobin level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
Reticulocyte count (10^9/L)	Mean (SD)	218 (75.0)	216 (69.1)
LDH level (U/L)	Mean (SD)	257.5 (97.6)	308.6 (284.8)
Total FACIT-Fatigue*	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)
Platelet count at screening <100 000/mm^3	n (%)	12 (29.3)	9 (23.1)
Platelet count at screening ≥100 000/mm^3	n (%)	29 (70.7)	30 (76.9)
History of aplastic anaemia	n (%)	11 (26.8)	9 (23.1)
History of myelodysplastic syndrome	n (%)	1 (2.4)	2 (5.1)

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

Pegcetacoplan was superior to eculizumab for the primary endpoint of the haemoglobin change from baseline (P<0.0001).

Figure 1. Adjusted mean change in haemoglobin (g/dL) from baseline to Week 16 in APL2-302



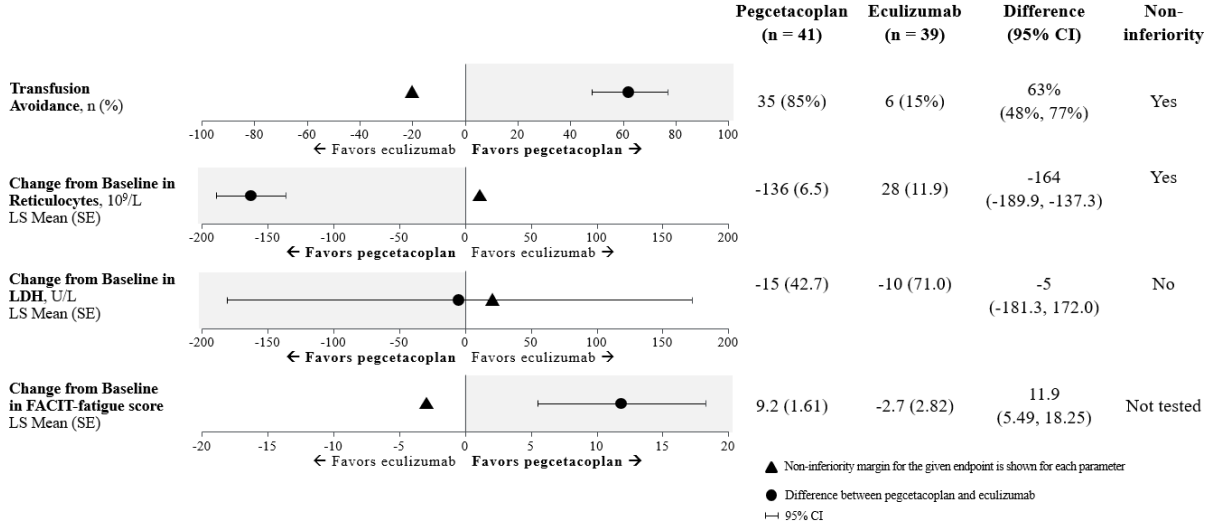
Non-inferiority was demonstrated in key secondary endpoints of transfusion avoidance and change from baseline in ARC.

Non-inferiority was not met in change from baseline in LDH.

Due to hierarchical testing, statistical testing for change from baseline for FACIT-Fatigue score was not formally tested.

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 APL2-302



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

Haemoglobin normalisation was achieved in 34% of patients in the pegcetacoplan group versus 0% in the eculizumab group at Week 16. LDH normalisation was achieved in 71% of patients in the group treated with pegcetacoplan versus 15% in the eculizumab group.

A total of 77 patients entered the 32-week OLP, during which all patients received pegcetacoplan, 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.

Study in complement inhibitor-naïve adult patients (APL2-308)

Study APL2-308 was an open-label, randomised, controlled study that enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrolment and with haemoglobin levels less than the lower limit of normal (LLN). Eligible patients were randomised in a 2:1 ratio to receive pegcetacoplan or supportive care (e.g., transfusions, corticosteroids, supplements such as iron, folate, and vitamin B12), hereafter referred to as the control arm through the duration of the 26-week treatment period.

Randomisation was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28 (<4; ≥4). At any point during the study, a patient assigned to the control arm who had haemoglobin levels ≥2 g/dL below baseline or presented with a PNH associated thromboembolic event was per protocol able to transition to pegcetacoplan for the remainder of the study.

A total of 53 patients were randomised, 35 to pegcetacoplan and 18 patients to the control arm. Demographics and baseline disease characteristics were generally well balanced between treatment arms. The mean age was 42.2 years in the pegcetacoplan arm and 49.1 years in the control arm. The mean number of PRBC transfusions in the 12 months prior to screening was 3.9 in the pegcetacoplan arm and 5.1 in the control arm. Five patients in each arm (14.3% in the pegcetacoplan arm and 27.8% in the control arm) had a history of aplastic anaemia. Further baseline values were as follows: mean

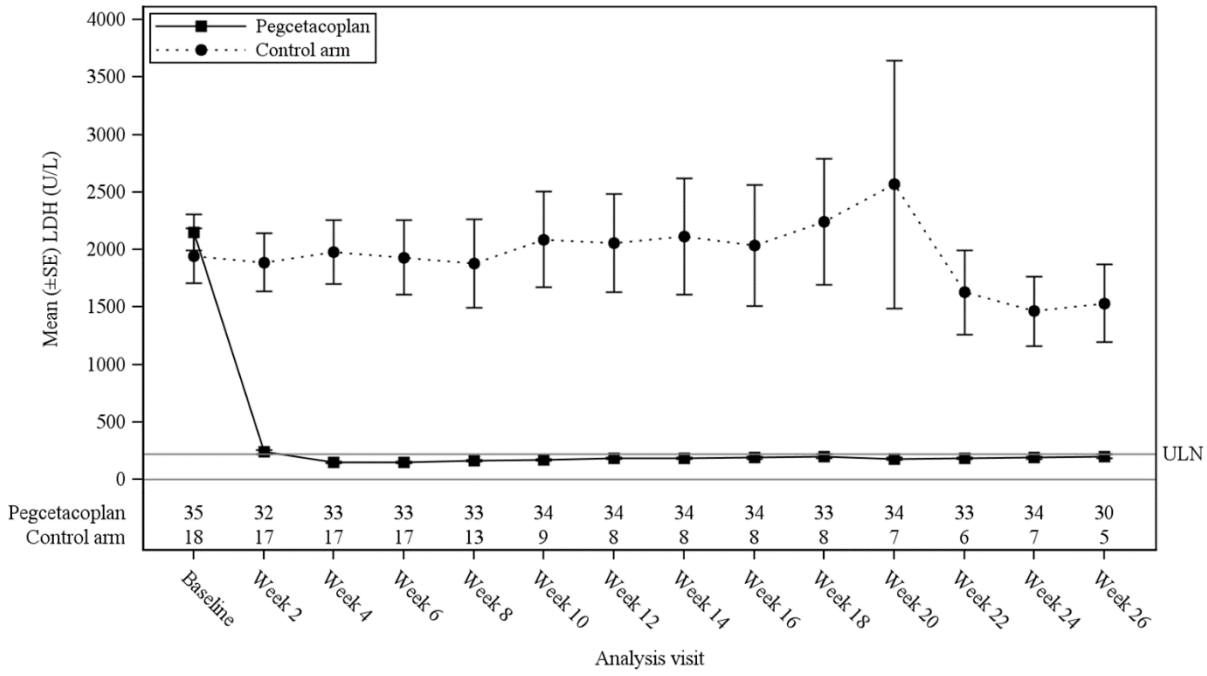
baseline haemoglobin levels (pegcetacoplan arm: 9.4 g/dL vs. control arm; 8.7 g/dL), ARC (pegcetacoplan arm: 230.2 × 10^9/L vs. control arm: 180.3 × 10^9/L), LDH (pegcetacoplan arm: 2 151.0 U/L vs. control arm: 1 945.9 U/L) and platelet count (pegcetacoplan arm: 191.4 × 10^9/L vs. control arm: 125.5 × 10^9/L). Eleven of 18 patients randomised to the control arm transitioned to pegcetacoplan because their haemoglobin levels decreased by ≥2 g/dL below baseline. Of the 53 randomised patients, 52 (97.8%) received prophylactic antibiotic therapy according to local prescribing guidelines.

The primary and secondary efficacy endpoints were assessed at Week 26. The two co-primary efficacy endpoints were haemoglobin stabilisation, defined as avoidance of a >1 g/dL decrease in haemoglobin concentration from baseline in the absence of transfusion, and change in LDH concentration from baseline.

In the group treated with pegcetacoplan, 30 out of 35 patients (85.7%) achieved haemoglobin stabilisation versus 0 patients in the control arm. The adjusted difference between pegcetacoplan and the control arm was 73.1% (95% CI, 57.2% to 89.0%; p<0.0001).

The least-square (LS) mean (SE) changes from baseline in LDH concentration at Week 26 were -1 870 U/L in the group treated with pegcetacoplan versus -400 U/L in the control arm (p<0.0001). The difference between pegcetacoplan and the control arm was -1 470 (95% CI, -2 113 to -827). Treatment differences between the pegcetacoplan and the control arm were evident at Week 2 and were maintained through Week 26 (Figure 3). LDH concentrations in the control arm remained elevated.

Figure 3. Mean (±SE) LDH concentration (U/L) over time by treatment group in study APL2-308



For the selected key secondary efficacy endpoints of haemoglobin response in the absence of transfusions, change in haemoglobin level, and change in ARC, the group treated with pegcetacoplan demonstrated a significant treatment difference versus the control arm (Table 3).

Table 3: Key secondary endpoints analysis in study APL2-308

Parameter	Pegcetacoplan (N=35)	Control arm (N=18)	Difference (95% CI) p-value
Haemoglobin response in the absence of transfusions[a] n (%)	25 (71%)	1 (6%)	54% (34%, 74%) p < 0.0001
Change from baseline to Week 26 in haemoglobin level (g/dL) LS Mean (SE)	2.9 (0.38)	0.3 (0.76)	2.7 (1.0, 4.4)
Change from baseline to Week 26 in ARC (10^9/L) LS Mean (SE)	-123 (9.2)	-19 (25.2)	-104 (-159, -49)

[a] Haemoglobin response was defined as a ≥1 g/dL increase in haemoglobin from baseline at Week 26.
ARC = Absolute reticulocyte count, CI = Confidence interval, LS = Least square, SE = Standard error

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ASPAVELI in one or more subsets of the paediatric population in paroxysmal nocturnal haemoglobinuria (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Pegcetacoplan is administered by subcutaneous infusion and gradually absorbed into the systemic circulation with a median T_{max} between 108 and 144 hours (4.5 to 6.0 days) following a single subcutaneous dose to healthy volunteers. Steady-state serum concentrations following twice weekly dosing at 1 080 mg in patients with PNH were achieved approximately 4 to 6 weeks following the first dose. In complement inhibitor-experienced patients (Study APL2-302) the geometric mean (%CV) steady-state serum concentrations ranged between 655 (18.6%) and 706 (15.1%) µg/mL in patients treated for 16 weeks. Steady-state concentrations in the patients (n=22) that continued to receive pegcetacoplan up to Week 48 were 623 µg/mL (39.7%), indicating sustainable therapeutic concentrations of pegcetacoplan through Week 48. In complement inhibitor-naïve patients (Study APL2-308) the geometric mean (%CV) steady-state serum concentration at Week 26 was 744 µg/mL (25.5%) with twice weekly dosing. The bioavailability of a subcutaneous dose of pegcetacoplan is estimated to be 76% based on population PK analysis.

Distribution
The mean (%CV) volume of distribution of pegcetacoplan is approximately 3.98 L (32%) in patients with PNH based on population PK analysis.

Metabolism/elimination
Based on its PEGylated peptide structure, the metabolism of pegcetacoplan is expected to occur via catabolic pathways and be degraded into small peptides, amino acids, and PEG. Results of a radiolabelled 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.

Pegcetacoplan showed no inhibition or induction of the CYP enzyme isoforms tested as demonstrated from the results of *in vitro* studies. Pegcetacoplan was neither a substrate nor an inhibitor of the human uptake or efflux transporters.

Following multiple subcutaneous dosing of pegcetacoplan in patients with PNH, the mean (%CV) clearance is 0.015 L/h (30%) and median effective half-life of elimination ($t_{1/2}$) is 8.6 days as estimated by the population PK analysis.

Linearity/non-linearity
Exposure of pegcetacoplan increases in a dose proportional manner from 45 to 1 440 mg.

Special populations
No impact on the pharmacokinetics of pegcetacoplan was identified with age (19-81 years), race or sex based on the results of population PK analysis.

Compared with a reference 70 kg patient, the steady-state average concentration is predicted to be approximately 20% higher in patients with a body weight of 50 kg. Patients weighing 40 kg are predicted to have a 45% higher average concentration. Minimal data are available on the safety profile of pegcetacoplan for patients with a body weight below 50 kg.

Elderly
Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 years and over is not sufficient to determine whether they respond differently from younger patients. See section 4.2.

Renal impairment
In a study of 8 patients with severe renal impairment, defined as creatinine clearance (CrCl) less than 30 mL/min using the Cockcroft-Gault formula (with 4 patients with values less than 20 mL/min), renal impairment had no effect on the pharmacokinetics of a single 270-mg dose of pegcetacoplan. There are minimal data on patients with PNH with renal impairment who have been administered the clinical dose of 1 080 mg twice weekly. There are no available clinical data for the use of pegcetacoplan in patients with ESRD requiring haemodialysis. See section 4.2.

5.3 Preclinical safety data

In vitro and *in vivo* toxicology data reveal no toxicity of special concern for humans. Effects observed in animals at exposure levels similar to clinical exposure levels are described below. These effects were not observed in clinical studies.

Animal reproduction
Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times the human steady-state C_{max}) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths. 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 foetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester, but the exposure was minimal (less than 1%, not pharmacologically significant).

Carcinogenesis
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 in an *in vitro* assay in human TK6 cells or in an *in vivo* micronucleus assay in mice.

Animal toxicology
Repeat-dose studies were conducted in rabbits and cynomolgus monkeys with daily subcutaneous doses of pegcetacoplan up to 7 times the human dose (1 080 mg twice weekly). Histologic findings in both species included dose-dependent epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues. These findings have been associated with large cumulative doses of long-chain PEG in other marketed PEGylated drugs, were without clinical consequence, and were not considered adverse. Reversibility was not demonstrated in the pegcetacoplan animal studies after one month and was not evaluated for a longer duration. Data from literature suggest reversibility of PEG vacuoles.

Renal tubular degeneration was observed microscopically in both species at exposures (C_{max} and AUC) less than or comparable to those for the human dose and was minimal and nonprogressive between 4 weeks and 9 months of daily administration of pegcetacoplan. Although no overt signs of renal dysfunction were observed in animals, the clinical significance and functional consequence of these findings are unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E 420)
Glacial acetic acid
Sodium acetate trihydrate
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Store in the original carton to protect from light.

6.5 Nature and contents of container

A Type I glass vial with a stopper (chlorobutyl or bromobutyl), and a seal (aluminium) with a flip-off cap (polypropylene) containing 54 mg/mL of sterile solution.

Each single pack contains 1 vial.

Multipack containing 8 (8 packs of 1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

ASPAVELI comes as a ready-to-use solution in single-use vials. Because the solution contains no preservative, this medicinal product should be infused immediately after preparing the syringe.

ASPAVELI is a clear, colourless to slightly yellowish aqueous solution. Do not use if the liquid looks cloudy, contains particles, or is dark yellow.

Always bring the vial to the room temperature for approximately 30 minutes before use.

Remove the protective flip cap from the vial to expose the central portion of the gray rubber stopper of the vial. Clean the stopper with a new alcohol wipe and allow the stopper to dry. Do not use if the protective flip cap is missing or damaged.

Preparing the syringe:

Option 1: If using a needleless transfer device (such as a vial adapter), follow the instructions provided by the device manufacturer.

Option 2: If transfer is done using a transfer needle and a syringe, follow the instructions below:
- Attach a sterile transfer needle to a sterile syringe.
- Pull back the plunger to fill the syringe with air, which should be about 20 mL.
- 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 centre of the vial stopper.
- The tip of the transfer needle should not be in the solution to avoid creating bubbles.
- Gently push the air from the syringe into the vial. This will inject the air from the syringe into the vial.
- Invert the vial.
- With the transfer needle tip in the solution, slowly pull the plunger to fill the syringe with the prescribed dose of ASPAVELI.
- Remove the filled syringe and the transfer needle from the vial.
- Do not recap the transfer needle. Unscrew the needle and throw it away in the sharps container.

Administration:

ASPAVELI should only be administered via subcutaneous administration using either a syringe system infusion pump or an on-body delivery system:

- Follow the device manufacturer's instructions to prepare the infusion pump and tubing. When using an infusion pump, areas for infusion include the abdomen, thighs, hips, or upper arms. Rotate infusion sites from one infusion to the next. If there are multiple infusion sites, they should be at least 7.5 cm apart. The infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site).

- Follow the device manufacturer's instructions to prepare the on-body delivery system. When using the on-body delivery system, ASPAVELI should be administered at a site on the abdomen. Rotate the infusion site from one infusion to the next. The infusion time varies by patient and typically ranges from 30 to 60 minutes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/001
EU/1/21/1595/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 December 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Swedish Orphan Biovitrum AB (publ)
Norra Stationsgatan 93
113 64 Stockholm
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The Marketing Authorisation Holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of ASPAVELI in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational and controlled distribution programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational and controlled distribution programme is aimed at:

- Ensuring patients receive vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* at least 2 weeks before starting treatment with ASPAVELI
- Ensuring that patients who cannot wait 2 weeks before starting treatment with ASPAVELI receive broad-spectrum antibiotics until 2 weeks after receiving the vaccines

- Ensuring that ASPAVELI is only dispensed after written confirmation that the patient has received vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or is receiving prophylactic antibiotic according to national guidelines
- Ensuring prescribers or pharmacists receive annual reminders of mandatory revaccinations in accordance with current national vaccination guidelines (including *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*)
- Providing information about the signs and symptoms of serious infections to healthcare providers and patients
- Ensuring that prescribers provide patients with the package leaflet and patient card and explain the main risks of ASPAVELI using these materials
- Ensuring that patients who experience symptoms of serious infections seek emergency medical treatment and present their patient card to the emergency care provider
- Educate prescribers and patients about the risk of IVH after discontinuation of the medicinal product and postponement of administration and the need to maintain effective complement inhibitor treatment
- Educate prescribers about the risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.

The MAH shall ensure that in each Member State where ASPAVELI is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use ASPAVELI have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The SmPC
- Guide for healthcare professionals
- Patient card

- **Guide for healthcare professionals:**
  - Treatment with ASPAVELI may increase the risk of serious infections with encapsulated bacteria.
  - The need for patients to be vaccinated against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or receive antibiotic prophylaxis.
  - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
  - Risk of IVH after discontinuation and postponement of administration of the medicinal product, its criteria, the required post-treatment monitoring, and its proposed management.
  - Risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.
  - The need to educate patients/carers of the following:
    - the risks of treatment with ASPAVELI
    - signs and symptoms of serious infections, hypersensitivity reactions, and what action to take
    - the patient/carer guides and its content
    - the need to carry the patient card and to tell any healthcare practitioner that he/she is receiving treatment with ASPAVELI
    - the requirement for vaccinations/antibiotic prophylaxis
    - the enrolment in the PASS
  - Instructions on how to handle possible adverse events.
  - Information about the PASS, the importance of contributing to such a study, and how to enter patients.
  - Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.

- **Patient card:**
  - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using ASPAVELI.
  - Signs or symptoms of the serious infections and warning to seek immediate attention from a healthcare professional if above is present.
  - Contact details of the ASPAVELI prescriber.

The patient information pack:
- Patient information leaflet
- Patient/carer guide

- **Patient/carer guide:**
  - Treatment with ASPAVELI may increase the risk of serious infections with encapsulated bacteria, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.
  - A description of the signs and symptoms of serious infections, hypersensitivity reactions, IVH after discontinuation of the medicinal product, and the need to seek emergency care at the nearest hospital.
  - The importance of vaccination prior to treatment with ASPAVELI and/or to receive antibiotic prophylaxis.
  - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
  - Detailed description of the modalities used for the self-administration of ASPAVELI.
  - Recommendation for use of effective contraception in women of childbearing potential.
  - Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.
  - Instructions on how to view the patient self-treatment video on any internet-connected device.
  - Enrolment in the PASS.

Annual reminder of mandatory revaccinations

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense ASPAVELI, a reminder in order that the prescriber/pharmacist checks if a re-vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* is required for his/her patients on treatment with ASPAVELI, in accordance with national vaccination guidelines.

System for controlled distribution

The MAH shall ensure that in each Member State where ASPAVELI is marketed, a system aimed to control distribution beyond the level of routine risk minimisation measures is in place. The following requirement needs to be fulfilled before the product is dispensed.

- Submission of written confirmation, or equivalent as permitted by national legislation, of the patient's vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or prophylactic antibiotic treatment according to national vaccination guidelines.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING 1 VIAL

1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 20 mL vial contains 1 080 mg pegcetacoplan (54 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: sorbitol, glacial acetic acid, sodium acetate trihydrate, sodium hydroxide, and water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
For subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ASPAVELI 1 080 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING 8 VIALS

1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 20 mL vial contains 1 080 mg pegcetacoplan (54 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: sorbitol, glacial acetic acid, sodium acetate trihydrate, sodium hydroxide, and water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
8 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
For subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ASPAVELI 1 080 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE INNER PACKAGING

INNER CARTON CONTAINING 1 VIAL

1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 20 mL vial contains 1 080 mg pegcetacoplan (54 mg/mL)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 vial. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
For subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ASPAVELI 1 080 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan
For subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ASPAVELI is and what it is used for

What is ASPAVELI
ASPAVELI 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 is ASPAVELI used for
ASPAVELI is used to treat adult patients with a disease called paroxysmal nocturnal haemoglobinuria (PNH) who have anaemia as a result of this disease.

In patients with PNH, the 'complement system' is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction, and blood clots. By attaching to and blocking the C3 protein, this medicine can stop the complement system from attacking red blood cells and so control symptoms of the disease. This medicine has been shown to increase the number of red blood cells (reduce anaemia), which may improve these symptoms.

2. What you need to know before you use ASPAVELI

Do not use ASPAVELI
- if you are allergic to pegcetacoplan or any of the other ingredients of this medicine (listed in section 6).
- if you have an infection caused by so-called encapsulated bacteria.
- if you are not vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using ASPAVELI.

Symptoms of infection
Before starting ASPAVELI, inform your doctor if you have any infections.

Because the medicine targets the complement system, which is part of the body's defences against infection, the use of this medicine increases your risk of infections, including those caused by the so-called encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. These are severe infections affecting your nose, throat and lungs or the linings of the brain and can spread throughout the blood and body.

Talk to your doctor before you start ASPAVELI to be sure that you receive vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* if you have not had these vaccines in the past. If you have had these vaccines in the past, you might still need additional vaccinations before starting this medicine. These vaccinations should be given at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection for 2 weeks after you have been vaccinated. Following vaccination, you may be more closely monitored by your doctor for symptoms of infection.

<u>Infection symptoms</u>
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache and a fever
- fever and a rash
- fever with or without shivers or chills
- shortness of breath
- high heart rate
- clammy skin
- headache with a stiff neck or stiff back
- headache with nausea (feeling sick) or vomiting
- eyes sensitive to light
- muscle aches with flu-like symptoms
- confusion
- extreme pain or discomfort

Make sure that you keep your vaccinations up to date. You should also be aware that vaccines reduce the risk of serious infections, but do not prevent all serious infections. In accordance with national recommendations, your doctor might consider that you need supplementary measures such as antibacterial medicines to prevent infection.

Allergic reactions
Allergic reactions may appear in some patients. In case of severe allergic reaction, discontinue ASPAVELI infusion and seek medical help immediately. Severe allergic reaction may present as difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing or collapse.

Injection site reactions
Injection site reactions have been observed with the use of ASPAVELI. You should undergo appropriate training in proper injection technique before self-administering.

Laboratory monitoring
During your treatment with ASPAVELI your doctor will perform regular check-ups, including blood tests for lactate dehydrogenase (LDH) levels and tests of renal function, and may adjust your dose if needed.

Effects on laboratory tests
Use of silica reagents in coagulation tests should be avoided as it can result in artificially prolonged activated partial thromboplastin time (aPTT).

Children and adolescents
Do not give this medicine to children under 18 years of age as no data are available on its safety and effectiveness in this group.

Other medicines and ASPAVELI
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility
Women of childbearing potential
The effects of the medicine on an unborn child are not known. The use of effective contraception methods is recommended during treatment and up to 8 weeks after treatment by women who are able to get pregnant. Ask your doctor for advice before taking this medicine.

Pregnancy/breast-feeding
ASPAVELI is not recommended during pregnancy and breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

ASPAVELI contains sorbitol
Sorbitol is a source of fructose. If your doctor has told you that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you take or receive this medicine.

ASPAVELI contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How to use ASPAVELI

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

At least 2 weeks before you start treatment with this medicine, your doctor 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 ASPAVELI, to reduce the risk of infection, your doctor will prescribe antibiotics for 2 weeks after you have been vaccinated.

Dose
The initial recommended dose for adults with PNH is 1 080 mg twice a week. You should take the twice weekly dose on Day 1 and Day 4 of each treatment week.

If you are switching to ASPAVELI from another type of PNH medicine, called a C5 inhibitor, you should take ASPAVELI in addition to your current dose of C5 inhibitor as prescribed for 4 weeks. After 4 weeks you should stop taking your C5 inhibitor.

The dose or dosing interval should not be changed without consulting your doctor. Your doctor may adjust your dose to 1 080 mg every third day (e.g., Day 1, Day 4, Day 7, Day 10, Day 13, and so forth) if appropriate. If you think you have missed a dose, speak to your doctor as soon as possible.

Method and route of administration
ASPAVELI is intended to be given as an infusion under the skin using:
- an infusion pump or
- an on-body delivery system.

Your first doses of the medicine will be given to you by healthcare professionals in a clinic or treatment centre. If treatment goes well, your doctor may discuss with you the possibility of you giving the medicine yourself at home. If this is appropriate, a healthcare professional will train you or a caregiver how to give the infusion.

Infusion rate(s)
Using the infusion pump, the infusion time is approximately 30 minutes if you use 2 infusion sites or approximately 60 minutes if using 1 site.

Using the on-body delivery system, the infusion time typically ranges from 30 to 60 minutes (depending on how quickly the medicine flows into your body).

The infusion should be started promptly after drawing this medicinal product into the syringe and completed within 2 hours after preparing the syringe.

Instructions for use – preparing the syringe

<table>
<tr>
<td>Step 1</td>
<td>
Prepare for infusion
Before you start:
1. Remove a single vial carton from the refrigerator. Keep the vial in the carton at room temperature and allow it to warm up for approximately 30 minutes. Do not try to speed up the warming process using a microwave or any other heat source.
2. Find a well-lit, flat work surface area, like a table.
3. Gather your supplies:
i) When using an infusion pump (Figure 1):
A. Syringe system infusion pump and manufacturer’s instructions (not shown)
B. Compatible syringe
C1. Transfer needle OR
C2. Needleless transfer device to draw up product from the vial
D. Infusion set (not shown; varies according to device manufacturer’s instructions)
E. Infusion tubing and Y connector (if required)
F. Sharps container
G. Alcohol wipes
H. Gauze and tape, or transparent dressing

OR

ii) When using an on-body delivery system (Figure 2):
A. On-body delivery system and manufacturer´s instructions (not shown)
B. Compatible syringe
C1. Transfer needle OR
C2. Needleless transfer device to draw up product from the vial
F. Sharps container
G. Alcohol wipes

Thoroughly clean your work surface using an alcohol wipe.

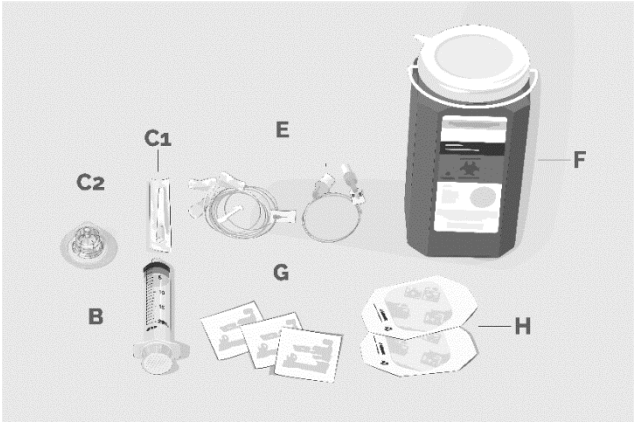
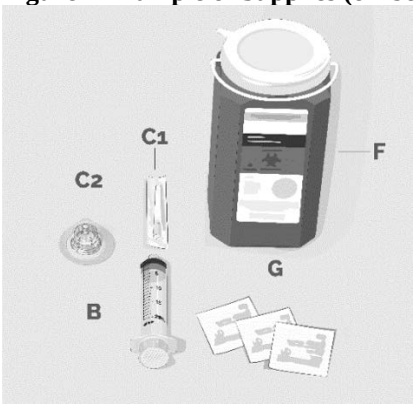
Wash your hands thoroughly with soap and water. Dry your hands.
</td>
<td>
Figure 1 Example of Supplies (infusion pump)


Figure 2 Example of Supplies (on-body delivery system)


</td>
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</table>

Step 2	**Check the vial and liquid** Remove the vial from the carton. Carefully look at the liquid in the vial. ASPAVELI is a clear, colourless to slightly yellowish liquid. Check for particles or colour changes (Figure 3). **Do not use the vial if:** • The liquid looks cloudy, contains particles, or is dark yellow. • The protective flip cap is missing or damaged. • The expiry date (EXP) on the label has passed.	**Figure 3** 

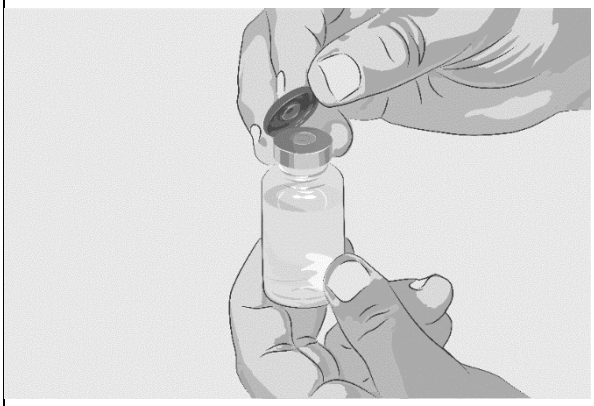
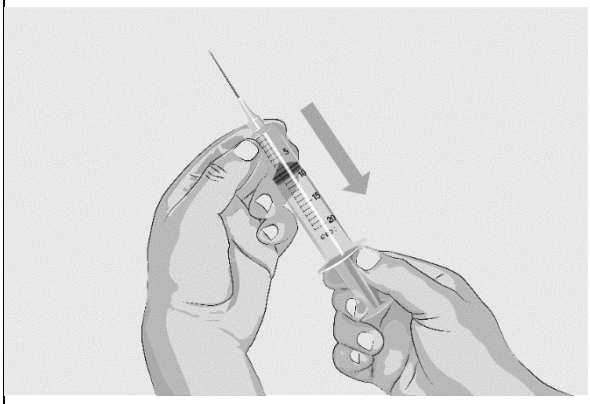
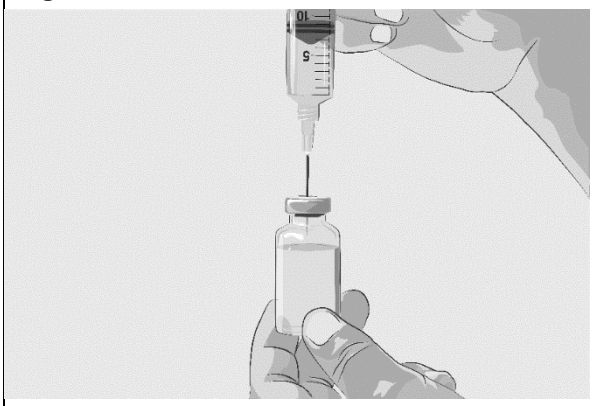
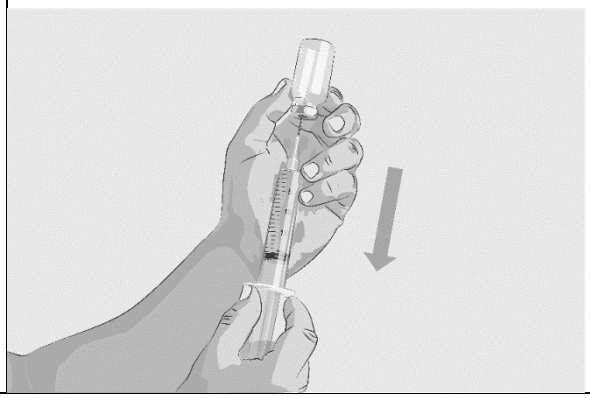
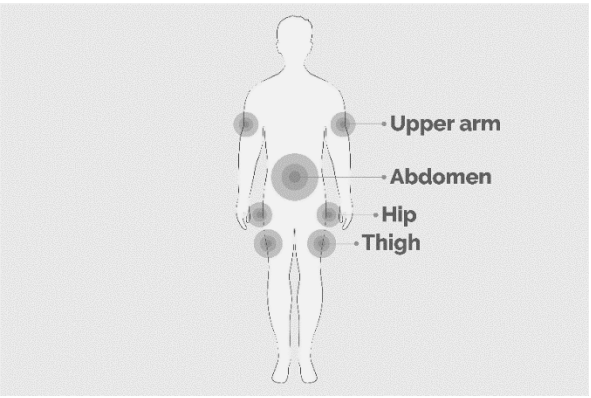
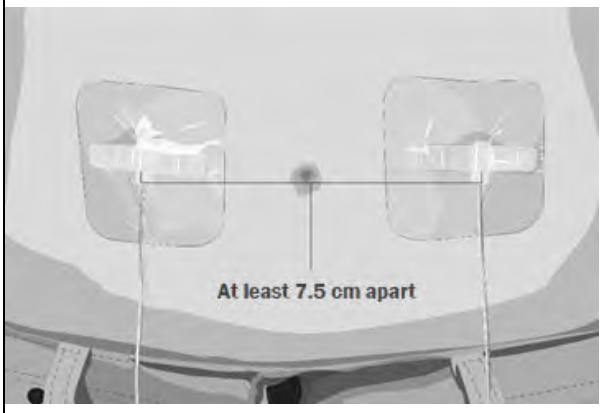
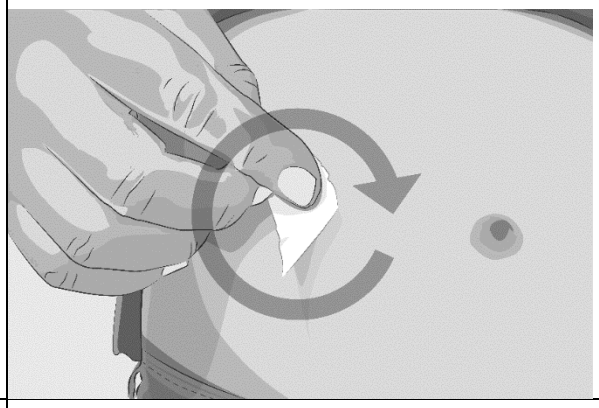
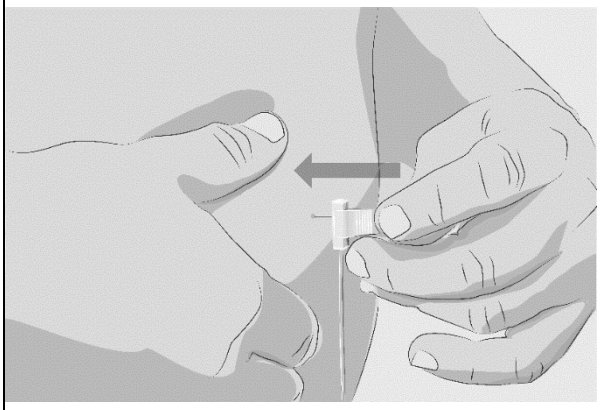
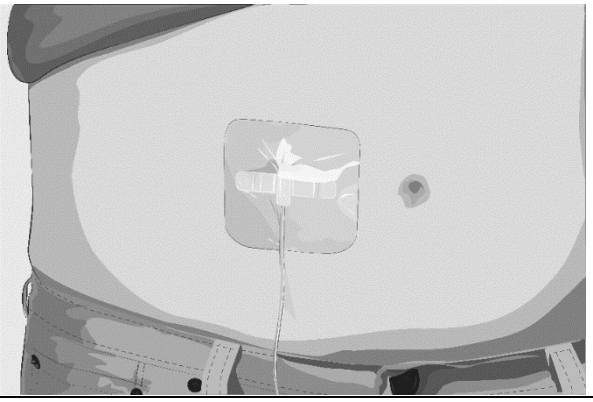
Step 3	**Prepare and fill syringe** Remove the protective flip cap from the vial to expose the central portion of the grey rubber stopper of the vial (Figure 4). Throw the cap away. Clean the stopper with a new alcohol wipe and allow the stopper to dry. Option 1: If using a needleless transfer device (such as a vial adapter), follow the instructions provided by the device manufacturer. OR Option 2: If using a transfer needle and a syringe, follow the instructions below: A. Attach a sterile transfer needle to a sterile syringe. B. Pull back the plunger to fill the syringe with air, which should be about 20 mL (Figure 5). C. Make sure the vial is in upright position. Do NOT turn the vial upside down. Push the air-filled syringe with the transfer needle attached through the centre of the vial stopper. D. The tip of the transfer needle should not be in the solution to avoid creating bubbles. (Figure 6). E. Gently push the air from the syringe into the vial. This will inject the air from the syringe into the vial. F. Turn the vial upside down (Figure 7). G. With the transfer needle tip in the solution slowly pull the plunger to fill the syringe with the prescribed dose of ASPAVELI (Figure 8). H. Remove the filled syringe and the transfer needle from the vial. I. **Do not recap the transfer needle.** Unscrew the needle and throw it away in the sharps container.	**Figure 4**  **Figure 5**  **Figure 6**  **Figure 7** 

		Figure 8 

For infusion of the product using an on-body delivery system, follow the device manufacturer's instructions. Throw away all used disposable supplies as well as any unused product and the empty vial as recommended by your healthcare professional.

For infusion of the product using a syringe system infusion pump, follow the steps below.

Step 4	**Prepare syringe system infusion pump and tubing** Gather the infusion pump supplies and follow the device manufacturer's instructions to prepare the pump and tubing.	
Step 5	**Prepare the infusion site(s)** A. Select an area on your abdomen (except for the five centimetres area around the belly button), thighs, hips, or upper arms region for the infusion(s) (Figure 9). B. Use a different site(s) from the one you used for your last infusion. If there are multiple infusion sites, they should be at least 7.5 cm apart. Rotate infusion sites in between each infusion (Figure 10). **C. Avoid the following infusion areas:** **a. Do not infuse into areas where the skin is tender, bruised, red, or hard.** **b. Avoid tattoos, scars, or stretch marks.**	**Figure 9**  **Figure 10** 

	D. Clean the skin at each infusion site(s) with a new alcohol wipe, starting at the centre and working outward in a circular motion (Figure 11). E. Let the skin dry.	**Figure 11** 
Step 6	**Insert and secure the infusion needle(s)** A. Pinch the skin between your thumb and forefinger around the infusion site (where you intend to place the needle). Insert the needle into the skin (Figure 12). Follow the device manufacturer's instructions on the angle of the needle. B. Secure the needle(s) using sterile gauze and tape or a transparent dressing placed over the infusion site(s) (Figure 13).	**Figure 12**  **Figure 13** 
Step 7	**Start infusion** Follow the device manufacturer's instructions to start the infusion. Start the infusion promptly after drawing the solution into the syringe.	
Step 8	**Complete infusion** Follow the device manufacturer's instructions to complete the infusion.	
Step 9	**Record infusion** Record your treatment as directed by your healthcare professional.	

Step 10	**Clean up** A. After the infusion is complete, remove the dressing and slowly take out the needle(s). Cover the infusion site with a new dressing. B. Disconnect the infusion set from the pump and discard into the sharps container (Figure 14). C. Throw away all used disposable supplies as well as any unused product and the empty vial as recommended by your healthcare professional. D. Clean and store the syringe system infusion pump according to the device manufacturer's instructions.	**Figure 14** 

If you forget to use ASPAVELI
If you miss a dose, it should be taken as soon as possible; then take the next dose at the regularly planned time.

If you stop using ASPAVELI
PNH is a lifelong condition and so it is expected that you will use this medicine for a long time. If you wish to stop using the medicine, please speak to your doctor first. If you stop taking the medicine suddenly, you may be at risk of making your symptoms worse.

If your doctor decides to stop your treatment with this medicine, follow their instructions for how to stop. Your doctor will monitor you closely for at least 8 weeks after stopping treatment for any signs of the destruction of red blood cells (haemolysis) due to PNH. Symptoms or problems that can happen due to destruction of red blood cell include:
- tiredness
- shortness of breath
- blood in the urine
- stomach-area (abdomen) pain
- drop in the number of your red blood cell count
- blood clots (thrombosis)
- trouble swallowing
- erectile dysfunction in males

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of ASPAVELI with you before treatment.

The most serious side effect is serious infection.

If you experience any of the infection symptoms (see section 2 "Infection symptoms"), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):
- Reactions at the site of injection: These include redness (erythema), swelling, itching (pruritus), bruising and pain. These reactions usually go away within a few days.
- Infection of the nose, throat, or airways (upper respiratory tract infection)
- Diarrhoea
- Destruction of red blood cells (haemolysis)
- Stomach pain (abdominal pain)
- Headache
- Tiredness (fatigue)
- Fever or high temperature (pyrexia)
- Cough
- Urinary tract infection
- Complications related to the mandatory vaccinations
- Arm and leg pain (pain in extremities)
- Dizziness
- Joint pain (arthralgia)
- Back pain

Common (may affect up to 1 in 10 people):
- Reaction at the site of injection, such as redness, or hardening of the skin
- Infection in the ear, mouth or skin
- Pain in the throat
- Fewer platelets in the blood (thrombocytopenia) which may cause bleeding or bruising more easily than normal
- Nausea (feeling sick)
- Decreased levels of potassium in the blood (hypokalaemia)
- Nose bleed (epistaxis)
- Skin redness (erythema)
- Muscle pain (myalgia)
- Infection of the stomach and intestines, which may cause symptoms of mild to severe nausea, vomiting, cramps, diarrhoea (gastrointestinal infection)
- Elevated liver tests
- Difficulty breathing (dyspnoea)
- Fewer number of white blood cells (neutropenia)
- Impaired kidney function
- Different colour of the urine
- High blood pressure
- Muscle spasms
- Stuffy nose (nasal congestion)
- Rash
- Infection in the blood (sepsis)
- Viral infection
- Fungal infection
- Respiratory tract infection
- Eye infection
- Hives
- COVID-19
- Bacterial infection
- Vaginal infection

Uncommon (may affect up to 1 in 100 people):
- Inflammation of the cervix
- Groin infection
- Pocket of pus in nose (nasal abscess)
- Pneumonia
- Tuberculosis
- Yeast infection in the esophagus

- Pocket of pus in anus (anal abscess)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ASPAVELI

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C – 8 °C).
- Keep the vial in the original carton in order to protect it from light.
- Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ASPAVELI contains
The active substance is pegcetacoplan 1 080 mg (54 mg/mL in a 20 mL vial).

The other ingredients are: sorbitol (E 420) (see section 2 "ASPAVELI contains sorbitol"), glacial acetic acid, sodium acetate trihydrate (see section 2 "ASPAVELI contains sodium"), sodium hydroxide (see section 2 "ASPAVELI contains sodium"), and water for injection.

What ASPAVELI looks like and contents of the pack
ASPAVELI is a clear, colourless to slightly yellowish solution for subcutaneous infusion (54 mg/mL in a 20 mL vial). Solutions that are cloudy or have particles or colour change should not be used.

Pack sizes
ASPAVELI comes in a pack of 1 vial or a multipack of 1 x 8 vials.

Please note that alcohol swabs, needles, and other supplies or equipment are not contained in the pack.

Not all pack sizes may be marketed.

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

Manufacturer
Swedish Orphan Biovitrum AB (publ)
Norra Stationsgatan 93
113 64 Stockholm
Sweden

This leaflet was last revised in MM/YYYY.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.