6.05 PEGCETACOPLAN,
Solution for subcutaneous infusion 1,080 mg in 20 mL,
Empaveli®,
SWEDISH ORPHAN BIOVITRUM PTY LTD.

1. Purpose of submission
	1. The Category 2 submission requested an amendment to the existing Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) to allow initial treatment with pegcetacoplan in patients who are either treatment-naïve to complement 5 inhibitors (C5is) or currently treated with a C5i.
	2. Listing was requested on the basis of a cost-minimisation approach (CMA) versus ravulizumab as initial treatment in patients diagnosed with PNH who are C5i-naïve.

Table 1: **Key components of the clinical issue addressed by the submission**

|  |  |
| --- | --- |
| Component | Description |
| Population | Adult (≥18 years old) patients with paroxysmal nocturnal haemoglobinuria (PNH) |
| Intervention | Pegcetacoplan (Empaveli) 1,080 mg/20 mL twice weekly subcutaneous dose\* delivered by a commercially available infusion pump |
| Comparator | Complement C5 inhibitor therapies, including eculizumab (Soliris®) and ravulizumab (Ultomiris®)a |
| Outcomes | Change in baseline haemoglobin level, rate of haemoglobin stabilisation, lactate dehydrogenase level, transfusion avoidance, transfusion requirements, rate of breakthrough haemolysis, quality of life and MAVEs |
| Clinical claim | In adults with PNH, pegcetacoplan significantly improves haemoglobin level and is at least non-inferior to complement C5 inhibitor in terms of efficacy and safety |

Source: Table 1-1; p12 of the submission

MAVE = major adverse vascular event

a In the “Intervention and comparator” subsection in Section 1.1 and in Section 2 of the main submission, ravulizumab was nominated as the primary comparator.

\*ESC noted this dosing regimen may be changed to 1,080 mg every third day if a patient has a lactate dehydrogenase (LDH) level greater than 2 × upper limit of normal (ULN).

1. Background

Registration status

* 1. Pegcetacoplan was approved by the TGA for treatment of adult patients with PNH who have an inadequate response to, or are intolerant of, a C5i, in February 2022. In July 2024, pegcetacoplan was submitted to the TGA for an extended registration of use in PNH patients, irrespective of line of treatment. The TGA Approval letter dated 28 January 2025 was received during the evaluation. Pegcetacoplan (Empaveli®) was registered for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) on 25 February 2025.
	2. It was noted that the draft product information for pegcetacoplan included a boxed warning regarding the risk of serious infections caused by encapsulated bacteria, such as Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type B (HIB), with recommendations to vaccinate against these bacteria prior to initiation of pegcetacoplan treatment. The ESC noted ATAGI advice would be required to extend access on the National Immunisation Program (NIP) to these vaccines for the requested extended PBS listing, as pegcetacoplan access to the vaccines on the NIP reflected use in second-line PNH[[1]](#footnote-2).
1. Requested listing

**Requested listing – initiating in complement C5i-naive patient**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **Dispensed Price for Max. Qty (public)** | **Dispensed Price for Max. Qty (private)** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| Pegcetacoplan; Classic PNH; Solution for subcutaneous infusion; 1,080 mg/20 mL; 20 mL | Published: $4,343.86Effective: $||||b  | Published:$4,392.53aEffective: $||||b | 1 | 1 | 0 | Empaveli® |
| **Category / Program**: Section 100 – Highly Specialised Drugs Program (Public/Private hospital) |
| **Prescriber type**: [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists [ ] Midwives |
| **Restriction type**:[ ] Unrestricted benefit[ ] Restricted benefit[ ] Authority Required (STREAMLINED) [ ] Authority Required (telephone/online PBS Authorities system) [x] Authority Required - nonimmediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as ‘FULL’ for full assessment by Services Australia) |
| **Treatment Phase**: initial (complement inhibitor inexperienced) |
| Clinical criteria:Patient must not have received prior treatment with this drug for this condition,ANDPatient must have PNH granulocyte clone size equal to or greater than 10% within the last 3 months,ANDPatient must not have received treatment with a complement inhibitor within 3 months prior to initiating treatment with this drug. |
| Treatment criteria: Must be treated by a haematologist, ORMust be treated by a non-specialist medical physician who has consulted a haematologist on the patient’s drug treatment details. |
| **Population criteria**: Patient must be at least 18 years of age |
| Caution: This drug increases the risk of encapsulated bacterial infections.Consult the approved PI for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection. |

Source: Table 1-10, pp28-29 of the submission

PNH = paroxysmal nocturnal haematuria

a The published dispensed price in a private hospital setting has been updated using the current markup and dispensing fee.

b The sponsor requested the same effective price for pegcetacoplan as it is currently listed on the PBS. The effective dispensed price in a private hospital setting has been updated using the current markup and dispensing fee.

**Requested listing – initiating in complement C5i-experienced patient**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **Dispensed Price for Max. Qty (public)** | **Dispensed Price for Max. Qty (private)** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| Pegcetacoplan; Classic PNH; Solution for subcutaneous infusion; 1,080 mg/20 mL; 20 mL | Published: $4,343.86Effective: $||||b | Published:$4,392.53aEffective: $||||b | 1 | 1 | 0 | Empaveli® |
| **Category / Program**: Section 100 – Highly Specialised Drugs Program (Public/Private hospital) |
| **Prescriber type**: [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists [ ] Midwives |
| **Restriction type**:[ ] Unrestricted benefit[ ] Restricted benefit[ ] Authority Required (STREAMLINED) [ ] Authority Required (telephone/online PBS Authorities system) [x] Authority Required - nonimmediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as ‘FULL’ for full assessment by Services Australia) |
| **Treatment Phase**: initial (complement inhibitor experienced) |
| Clinical criteria:Patient must not have received prior treatment with this drug for this condition,ANDPatient must have PNH granulocyte clone size equal to or greater than 10% within the last 3 months,ANDPatient must have received treatment with at least one C5i for at least 3 months before initiating treatment with this drug unless intolerance of severity necessitating permanent treatment withdrawal had occurred,ANDThe treatment must be in combination with one PBS-subsidised C5 inhibitor for a period of 4 weeks during initiation of therapy.  |
| Treatment criteria: Must be treated by a haematologist, ORMust be treated by a non-specialist medical physician who has consulted a haematologist on the patient’s drug treatment details. |
| **Population criteria**: Patient must be at least 18 years of age |
| Caution: This drug increases the risk of encapsulated bacterial infections.Consult the approved PI for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection. |

Source: Table 1-9, p28 of the submission

C5i = complement 5 inhibitor; PNH = paroxysmal nocturnal haematuria

a The published dispensed price in a private hospital setting has been updated using the current markup and dispensing fee.

b The sponsor requested the same effective price for pegcetacoplan as it is currently listed on the PBS. The effective dispensed price in a private hospital setting has been calculated using the current markup and dispensing fee.

**Requested listing – first continuing**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **Dispensed Price for Max. Qty (public)** | **Dispensed Price for Max. Qty (private)** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| Pegcetacoplan; Classic PNH; Solution for subcutaneous infusion; 1,080 mg/20 mL; 20 mL | Published: $4,343.86Effective: $||||b | Published:$4,392.53aEffective: $||||b | 1 | 1 | 5 | Empaveli® |
| **Category / Program**: Section 100 – Highly Specialised Drugs Program (Public/Private hospital) |
| **Prescriber type**: [ ] Dental [x] Medical Practitioners [ ] Nurse practitioners [ ] Optometrists [ ] Midwives |
| **Restriction type**:[ ] Unrestricted benefit[ ] Restricted benefit[ ] Authority Required (STREAMLINED) [ ] Authority Required (telephone/online PBS Authorities system) [x] Authority Required - nonimmediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as ‘FULL’ for full assessment by Services Australia) |
| Clinical criteria:Patient must have received PBS-subsidised treatment with this drug for PNH under the ‘Initial (complement inhibitor experienced)’ or ‘Initial (complement inhibitor inexperienced)’ or ‘Grandfather’ treatment restriction,ANDThe treatment must not be in combination with a C5i |
| Treatment criteria: Must be treated by a haematologist, ORMust be treated by a non-specialist medical physician who has consulted a haematologist on the patient’s drug treatment details. |
| **Population criteria**: Patient must be at least 18 years of age |
| Caution: This drug increases the risk of encapsulated bacterial infections.Consult the approved PI for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection. |

Source: Table 1-11, p29 of the submission

C5i = complement 5 inhibitor; PNH = paroxysmal nocturnal haematuria

a The published dispensed price in a private hospital setting has been updated using the current markup and dispensing fee.

b The sponsor requested the same effective price for pegcetacoplan as it is currently listed on the PBS. The effective dispensed price in a private hospital setting has been calculated using the current markup and dispensing fee.

**Requested listing – subsequent continuing**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **Dispensed Price for Max. Qty (public)** | **Dispensed Price for Max. Qty (private)** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| Pegcetacoplan; Classic PNH; Solution for subcutaneous infusion; 1,080 mg/20 mL; 20 mL | Published: $4,343.86Effective: $||||b | Published:$4,392.53aEffective: $||||b | 1 | 1 | 5 | Empaveli® |

a The published dispensed price in a private hospital setting has been updated using the current markup and dispensing fee.

b The sponsor requested the same effective price for pegcetacoplan as it is currently listed on the PBS. The effective dispensed price in a private hospital setting has been calculated using the current markup and dispensing fee.

* 1. The requested initiation restrictions included the following patient groups: (1) adult patients with confirmed PNH who have not received any C5i therapy within 3 months before the initiation of pegcetacoplan, (2) adult patients with confirmed PNH who have been receiving a C5i treatment for at least 3 months before the initiation of pegcetacoplan, but switching from C5i to pegcetacoplan at the treating clinicians and patients’ discretion, regardless of the response to the current C5i therapy, and (3) adult patients with PNH, both C5i-naïve and experienced, who are currently receiving pegcetacoplan as treatment.
	2. The submission proposed a published dispensed price of $4,343.86 for public hospital and $4,392.23 for private hospital. The submission requested the same effective price for pegcetacoplan as was currently in place for second-line use of pegcetacoplan ($||| ||| for public hospital and $||| ||| for private hospital). The current PBS restriction for initiation of pegcetacoplan treatment in C5i-experienced patients who show inadequate response or intolerance to the C5i is associated with a Special Pricing Arrangement (SPA) to ensure pegcetacoplan is cost-neutral for those switching from C5is. There is a ||| |||% price rebate (via SPA) for ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| when pegcetacoplan is used in addition to C5i treatment. The submission continued to request a SPA for the initiation of the drug in patients switching from a C5i as determined by their treating clinicians, regardless of their response to the C5i therapy.
	3. The proportion of PNH patients who would switch to pegcetacoplan from the current C5i treatment was uncertain and there was no restriction proposed for patients who switch. This has been clarified in proposed restriction changes, from the Secretariat, to an ‘Initial 1 treatment (complement inhibitor untreated patients)’ restriction with wording aligned with existing new untreated patient listings for ravulizumab and eculizumab, and an ‘Initial 2 (complement inhibitor experienced patients)’ restriction, with the removal of the haemoglobin threshold. For PNH patients who are C5i-naïve and less able to attend treatment centres / hospitals for intravenous (IV) infusions, there may be a preference for the use of pegcetacoplan due to the ability to self-administer.
	4. The PBS restrictions for ravulizumab and eculizumab require eligible patients to have at least one of the following: (1) experienced a thrombotic/embolic event that required anticoagulant therapy, (2) transfusion with ≥ 4 units of packed red blood cell (PRBC) in the prior 12 months, (3) chronic/recurrent anaemia with multiple haemoglobin measurements not exceeding 7.0 g/dL in the absence of anaemia symptoms, (4) chronic/recurrent anaemia with multiple haemoglobin measurements not exceeding 10 g/dL in addition to having anaemia symptoms, (5) debilitating shortness of breath/chest pain resulting in limitation of normal activity and/or established diagnosis of pulmonary arterial hypertension, (6) a history of renal insufficiency, demonstrated by an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73m2, or (7) recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia. These criteria were not included in the proposed restriction for pegcetacoplan. This may result in PNH patients with milder symptoms being treated with pegcetacoplan resulting in an expanded market. The cost-effectiveness of pegcetacoplan in patients with milder PNH symptoms was unknown. The ESC advised that the pegcetacoplan restriction should align with the C5i PBS listings for PNH. The pre-sub-committee response (PSCR) clarified that the removal of haemoglobin level criteria was intended for the ‘Initial 2 (switching from Complement 5 inhibitor)’ restriction; the ESC agreed with the Secretariat proposed changes to align with the C5i PBS restrictions and noted the PSCR agreed with Secretariat revised wording for ‘Initial 1’ and ‘Initial 2’ restrictions.
	5. The pre-PBAC response raised that the sponsor had recently initiated an early access program for patients who are naïve to C5i therapy and for patients who are C5i experienced with a haemoglobin level ≥10.5 g/dL. These patients would meet the eligibility criteria under the proposed PBS listing. As such, grandfather restrictions are requested for the two aforementioned indications, to allow these patients to transition to PBS-subsidised pegcetacoplan upon PBS listing. It was proposed that the clinical criteria for the Grandfather restriction align with the Continuing Treatment criteria.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Population and disease
	1. PNH is a rare, chronic, and life-threatening blood disease that is most often diagnosed in young adults 30 to 40 years of age. The disease has been reported worldwide and affects male and female equally. Some studies reported that PNH-associated thrombosis occurred more frequently in patients in the western countries (in up to 30% of patients with PNH) compared to in less than 15% of patients in Asian countries.[[2]](#footnote-3),[[3]](#footnote-4) The ESC advised the theory that patients from different ethnic groups have different thrombosis risks has been refuted by a study demonstrating no correlation, and hence treatment modification based on Asian decent was not clear. [[4]](#footnote-5) Furthermore, it was understood through a number of clinical studies that there is no clear difference in PNH phenotype across different ethnic groups.[[5]](#footnote-6) [[6]](#footnote-7) [[7]](#footnote-8)
	2. PNH occurs due to an acquired mutation in the phosphatidylinositol glycan A (PIG-A) gene which results in a lack of terminal complement inhibitor proteins (CD55 and CD59) on cell surfaces. Their absence in blood cells results in uncontrolled complement activation and systemic complications which include intravascular haemolysis, bone marrow dysfunction, and thrombosis.
	3. Confirmation of PNH utilises the flow cytometry to measure the percentage of CD55-negative and CD59-negative cells. Clinically, the manifestation of PNH is heterogeneous, with various degrees of thrombophilia (i.e., tendency of blood clot formation), haemolysis, haemoglobinuria, and bone marrow dysfunction. In classic PNH, patients typically present with clinically significant complement driven haemolysis. Other PNH associated symptoms include abdominal/back pain, oesophageal spasm, difficulty swallowing, and erectile dysfunction in males. Intravascular haemolysis also results in jaundice, haemoglobinuria, and elevated levels of lactate dehydrogenase (LDH). Anaemia-related symptoms include fatigue, weakness, and dyspnoea on exertion. Bone marrow failure in patients with classic PNH is uncommon and is usually a result of another concomitant bone marrow disorder (such as aplastic anaemia). Morbidities and mortality of PNH are mostly associated with complement driven intravascular haemolysis, thrombosis, and bone marrow failure.
	4. Before the availability of complement inhibitor therapy, PNH had been managed mainly by supportive care with repeated blood transfusions, anticoagulants, corticosteroids, and supplements including iron, folate, and vitamin B12. Haematopoietic stem cell transplantation has the potential for cure. However, this is rarely used as it is associated with a high level of morbidity and mortality (paragraph 4.2, pegcetacoplan PBAC public summary document (PSD), March 2022 PBAC meeting). Eculizumab was the first C5i available for treatment of PNH and has been proven to significantly reduce the risk of PNH associated thromboembolism and improve survival.[[8]](#footnote-9) Ravulizumab is a pharmacological analogue of eculizumab and was considered non-inferior to eculizumab in terms of efficacy and safety by the PBAC (para 6.50 and 6.51, ravulizumab PSD, July 2020 PBAC meeting). Ravulizumab is currently the mostly commonly used C5i for treatment of PNH in Australia. Pegcetacoplan is currently listed as the second-line treatment for PNH patients who demonstrate inadequate response or intolerance to C5i treatment.
	5. Neisseria meningitis or sepsis events are the most feared complications of C5i therapy. Patients on C5i showed a lifelong 1000-fold to 2000-fold increased incidence of meningococcal disease compared to healthy adults not under C5i therapy, despite rigorous vaccinations and penicillin prophylaxis.[[9]](#footnote-10)
	6. Most PNH patients receiving C5i treatment continue to experience complement C3-mediated extravascular haemolysis and anaemia related symptoms, and some are not transfusion independent or free of thromboembolic events despite a stable C5i dosing.[[10]](#footnote-11) Breakthrough haemolysis may continue to occur in patients receiving C5i.[[11]](#footnote-12)
	7. In the submission, pegcetacoplan was proposed to be (1) the first-line treatment of PNH in patients who have not received any C5i treatment, and (2) the alternative treatment for PNH in patients who are receiving C5i therapy but choose to switch from C5i at the discretion of the treating clinician and patients, regardless of the response to the C5i therapy.
	8. Pegcetacoplan is a polyethylene glycol (PEG) peptide that binds to and inhibits the proximal complement C3, thus reducing both C3-mediated extravascular haemolysis, as well as intravascular haemolysis from downstream complement activation.[[12]](#footnote-13) The proposed dose of pegcetacoplan is 1,080 mg in 20 mL solution administered twice weekly via subcutaneous (SC) infusion through a commercially available infusion pump. This dosing regimen may be changed to 1,080 mg every third day if a patient has a lactate dehydrogenase (LDH) level greater than 2 × upper limit of normal (ULN). Vaccinations against Streptococcus pneumoniae, Neisseria meningitidis types A, C, W, Y, B, and Haemophilus influenzae type B (HIB) are required within the previous two years or at least two weeks prior to receiving the first dose of pegcetacoplan. Patients transitioning from a C5i will be vaccinated but may need boosters.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Comparator
	1. Ravulizumab was nominated as the primary comparator in the submission. Ravulizumab is long-acting anti-C5 monoclonal antibody that antagonises terminal complement at the same C5 epitope as eculizumab, hence reducing the downstream complement-mediated intravascular haemolysis. Ravulizumab is administered as a weight-based dose via IV infusion at a frequency of once every 8 weeks. The main arguments provided in the submission in support of this nomination were: (1) the PBAC previously determined ravulizumab to be a pharmacological analogue of eculizumab and that ravulizumab is non-inferior to eculizumab in terms of efficacy and safety (para 6.50 and 6.51, ravulizumab PSD, July 2020 PBAC meeting), (2) the PBAC recommended that ravulizumab should be treated as interchangeable with eculizumab (para 7.18, ravulizumab PSD, July 2021 PBAC meeting), (3) the PBAC advised ravulizumab be listed based on a cost-minimisation to eculizumab (para 7.1, ravulizumab PSD, July 2021 PBAC meeting), and (4) as ravulizumab is dosed every 8 weeks the PBAC considered it would be the C5i most likely to be replaced in clinical practice now that it is PBS listed and hence the appropriate base case comparator for any future cost-minimisation analysis (para 7.9, pegcetacoplan PSD, March 2022 PBAC meeting). The ESC considered ravulizumab was the appropriate comparator.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Consideration of the evidence

Sponsor hearing

* 1. The sponsor requested a hearing for this item. The clinician presented a clinical case study, discussed the natural history of the disease, and presented data from a post hoc analysis of patients with baseline haemoglobin ≥ 100 g/L to show how pegcetacoplan can improve or normalise haematologic parameters and reduce fatigue in patients with PNH and mild or moderate anaemia[[13]](#footnote-14).” When the PBAC asked about the expected use in first-line versus second-line, the clinician was uncertain about the likely uptake in patients initiating treatment or switching early from a C5i, although it was expected most patients would continue to use a C5i first-line given familiarity with these therapies. Nonetheless, it was explained that an alternative to the IV infusions would be an important option for some patients. The PBAC considered the hearing highlighted that the primary role of pegcetacoplan would remain as a second-line treatment option for managing symptoms and haematological outcomes for patients not adequately responding to a C5i.

Consumer comments

* 1. The PBAC noted that no consumer comments were received for this item.

Clinical trials

* 1. No head-to-head trials were identified that directly compared pegcetacoplan vs ravulizumab in the proposed PBS target population. The submission was based on one randomised controlled trial (RCT) which compared pegcetacoplan to best supportive care (BSC) in treatment naïve PNH patients (PRINCE), and one RCT comparing ravulizumab to eculizumab in treatment naïve patients (ALXN1210-301), to inform the indirect treatment comparison (ITC) between pegcetacoplan and ravulizumab. The unanchored matching-adjusted indirect comparison (MAIC) method was used to compare the efficacy and safety data of the two trials[[14]](#footnote-15). The safety of pegcetacoplan and ravulizumab were compared without any adjustments.
	2. Details of the key trials presented in the submission are provided in Table 2.

Table 2: **Trials and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
| --- | --- | --- |
| PRINCE (NCT04085601) | APL2-308 PRINCE CSR October 2021. A phase 3, randomised, multicentre, open-label, controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria (PNH). Clinical Study Report. |  |
| Wong RSM, Navarro-Cabrera JR., Comia NS et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. | *Blood* *Advances* 2023; 7(11), 2468-2478. |
| A research study to gather scientific information about the efficacy and safety of the investigational drug APL-2 in treating patients with paroxysmal nocturnal hemoglobinuria (PNH), a disease associated with anaemia, in a randomly assigned comparison with the current standard of care approved for PNH.  |  |
| APL2-308 PRINCE Protocol August 2020. A phase 3, randomised, multicentre, open-label, controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria (PNH). Amendment 3. |  |
| Panse J, Daguindau N, Okuyama S et al. Improvements in hematologic markers and decreases in fatigue with pegcetacoplan for patients with paroxysmal nocturnal hemoglobinuria and mild or moderate anemia (hemoglobin ≥10 g/dL) who had received eculizumab or were naive to complement inhibitors. | *PLoS One* 2024; 19(7), e0306407 |
| Mulherin BP, Yeh M, Al-Adhami M & Dingli D. Normalization of hemoglobin, lactate dehydrogenase, and fatigue in patients with paroxysmal nocturnal hemoglobinuria treated with pegcetacoplan.  | *Drugs in R & D* 2024; 24(2), 169-177. |
| ALXN1210-301(NCT02946463) | Lee JW, Sicre de Fontbrune F, Wong Lee Lee et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. | *Blood* 2019; 133(6), 530-539 |
| ALXN-1210-301 Protocol March 2019. A phase 3, randomised, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naïve adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Amendment 5. |  |
| Brodsky RA, Peffault de Latour R, Rottinghaus ST et al. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. | *Haematologica* 2021; 106(1), 230-237. |
| Ishiyama, K., Nakao, S., Usuki, K et al. Results from multinational phase 3 studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria: subgroup analysis of Japanese patients. | International Journal of Hematology 2020; 114(4), 466-476. |
| Kulasekararaj A, Glasmacher A, Liu P et al. Composite endpoint to evaluate complement inhibition therapy in patients with paroxysmal nocturnal hemoglobinuria | European Journal of Haematology 2022; 108(5), 391-402. |
| Kulasekararaj AG, Griffin M, Langemeijer S et al. Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies. | European Journal of Haematology 2022; 109(3), 205-214. |
| Schrezenmeier H, Kulasekararaj A, Mitchell L et al. One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study. | Therapeutic Advances in Hematology 2020; 11, 2040620720966137. |
| Schwartz CE, Stark RB, Borowiec K & Myren KJ. No impact of Asian ethnicity on EORTC QLQ-C30 scores: Group differences and differential item functioning in paroxysmal nocturnal hemoglobinuria. | Health and Quality of Life Outcomes 2021; 19(1), 228. |
| Schwartz CE, Stark RB, Borowiec K et al. Norm-based comparison of the quality-of-life impact of ravulizumab and eculizumab in paroxysmal nocturnal hemoglobinuria | Orphanet Journal of Rare Diseases 2021; 16(1), 389. |
| Matching-adjusted indirect comparison of the PRINCE trial and ALXN-1210-301 | Wong R, Fishman J, Wilson K et al. Comparative effectiveness of pegcetacoplan versus ravulizumab and eculizumab in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria: A matching-adjusted indirect comparison. | *Advances in Therapy* 2023; 40(4), 1571-1589. |
| APL2-307 open-label extension (OLE) study (NCT03531255) | Griffin M, Kelly RJ, Panse J et al. Management of acute breakthrough hemolysis with intensive pegcetacoplan dosing in patients with PNH. | *Blood Advances* 2024; 8(7), 1776-1786. |
| Patriquin CJ, Bogdanovic A, Griffin M et al. Safety and efficacy of pegcetacoplan in adult patients with paroxysmal nocturnal hemoglobinuria over 48 weeks: 307 Open-Label Extension Study. | *Advances in Therapy* 2024; 41(5), 2050-2069. |

Source: Table 2-2, pp35-37 of the submission

CSR = clinical study report; PNH = paroxysmal nocturnal haemoglobinuria

* 1. The key features of the included evidence for the indirect comparison are summarised in Table 3.

Table 3: Key features of the included evidence (indirect comparison)

| **Trial** | **N** | **Design/duration** | **Risk of bias** | **Patient****population** | **Outcome(s)** |
| --- | --- | --- | --- | --- | --- |
| **Pegcetacoplan vs BSC**  |
| PRINCE | 53 | R, OL26 wks | Lowa,b | Adult PNH patients who were Ci naïve  | * Hb stabilisation (defined as the avoidance of a >1 g/dL decrease in Hb level from BS to Week 26
* LDH level change from BL at Week 26
* Hb response (defined as Hb increase ≥ 1g/dL from BL)
* Change from BL in absolute reticulocyte count
* Change from BL in Hb level
* Percentage of patients who received transfusion and/or had a > 2 g/dL decreased from BL in Hb level
* Transfusion avoidance during the 26 weeks
* Number of units of PRBC transfused during the 26 weeks
* Absolute reticulocyte count normalisation
* LDH normalisation
* Breakthrough haemolysisc
* Change in QoL from BL to Day183 (FACIT-Fatigue Scale score)
* Change in the EORTC-QLQ-C30 from BL
* Any TEAEs
* Serious AEs
 |
| **Ravulizumab vs eculizumab** |
| ALXN1210-301 | 246 | R, OL26 wks | Lowa,b | Adult PNH patients who were Ci naïve | * Transfusion avoidance (TA)
* Haemolysis as measured by LDH normalisation from Day 29 through Day 183
* Percentage of change of LDH from BL to Day 183
* Percentage of patients with breakthrough haemolysisc (≥ 1 new or worsening symptoms/signs of intravascular haemolysis, MAVEs in the presence of LDH ≥ 2 x ULN after prior reduction of LDH to < 1.5 x ULN on treatment
* Percentage of patients with stabilised Hb (no ≥ 2 g/dL decrease in Hb level from BL in the absence of transfusion)
* Number of units of PRBC transfused
* Change in QoL from BL to Day 183 (FACIT-Fatigue Scale)
* Change in the EORTC-QLQ-C30 from BL
* Percentage of patients experiencing MAVEsd
* Change in free C5 concentrations
* Any TEAEs
* Serious AEs
 |

Source: Complied during the evaluation based on information provided in Section 2.2-2.3 of the submission.

AE = adverse event; BSC = best supportive care; BL = baseline; Ci = complement inhibitor; EORTC = European Organisation for the Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; Hb = haemoglobin; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; PEG = pegcetacoplan; PMN = polymorphonuclear leukocyte; PNH = paroxysmal nocturnal hemoglobinuria; PRBC = packed red blood cell; QoL = quality of life; SC = subcutaneous; TEAE = treatment emergent adverse event; ULN = upper limit of normal

a Risk of bias was considered low for objective study endpoints. However, patient reported outcomes in the trial were subjected to bias due to the open-label design.

b Risk of bias of the indirect comparison was considered high due to the transitivity issues between the trials

c Defined as fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (Hb < 10 g/dL), history of major adverse vascular events (MAVEs) (including thrombosis), dysphagia, erectile dysfunction, or history of PRBC transfusions due to PNH

d Including thrombosis

* 1. PRINCE was a Phase 3, multicentre, open label, randomised controlled trial comparing pegcetacoplan (1,080 mg SC twice weekly) vs BSC, which included blood transfusions, corticosteroids, and supplements, in treatment naïve adult patients diagnosed with PNH. Fifty-three patients (N = 53) were enrolled in PRINCE; thirty-five patients were randomised to the pegcetacoplan arm (n = 35) and 18 to the BSC arm (n = 18). Patients randomised to the BSC arm were allowed to switch to pegcetacoplan if their haemoglobin levels decreased ≥ 2g/dL below their baseline measurement or if they had a qualifying thromboembolic event secondary to PNH. Pegcetacoplan dosage could be increased to 1,080 mg once every 3 days if LDH concentration was > 2 times the upper limit of normal (ULN) on one occasion following ≥ 4 weeks of treatment. The randomised controlled period (RCP) of treatment in PRINCE was 26 weeks. All patients who completed the 26-week allocated treatment rolled over into a separate open-label extension (OLE) study or completed the 8-week safety follow-up. There was a post-RCP period between the RCP and the initiation of the OLE study. During the post-RCP period, patients received the treatment they had been receiving during the RCP. Risk of bias was considered low for the objective study endpoints in PRINCE. However, endpoints involving clinical symptoms such as fatigue, as well as patient reported outcomes in the trial have the potential for bias due to the open-label study design. PRINCE was conducted in countries in Asia and South America and no Caucasians were included in the trial.
	2. ALXN1210-301 was a Phase 3, multicentre, open-label, active-controlled trial comparing ravulizumab vs eculizumab in treatment naïve adult patients diagnosed with PNH. There were 125 patients randomised to the ravulizumab arm and 121 to the eculizumab arm. In ALXN1210-301, patients received 26 weeks of randomised treatment, then ravulizumab extension treatment for up to 2 years. Risk of bias was considered low for the objective study endpoints in ALXN1210-301. However, there is potential for the patient reported outcomes to be biased because of the open-label study design.
	3. Key differences identified across the PRINCE and ALXN1210-301 trials include:
* Inclusion criteria: Patients had to present at least one PNH related symptom or sign within the 3 months before trial screening to be eligible for inclusion into ALXN1210-301. However, this was not required for patients to be included into PRINCE. As a result, ALXN1210-301 may have included patients with a higher disease severity compared to PRINCE. This was reflected by a higher number of PRBC transfusion received within the 12 months before study entry in ALXN1210-301 compared to PRINCE (see the third dot point below). While ALXN1210-301 only included PNH patients who were truly complement inhibitor naïve, PRINCE may have included patients who had had previous exposure to a complement inhibitor.
* Definition of endpoint: In PRINCE, haemoglobin stabilisation was defined as the avoidance of a > 1g/dL decrease in haemoglobin levels from baseline to end of RCP, while in ALXN1210-301, it was defined as the avoidance of ≥ 2 g/dL decrease in haemoglobin levels from baseline to end of RCP.
* Baseline patient characteristics: Before adjusting, the PRINCE population had a higher percentage of Asian, mean LDH level, and European Organisation for the Research and Treatment of Cancer (EORTC) — General Health status score at baseline compared to the ALXN1210-301 population. No Caucasians were enrolled in PRINCE. On the other hand, ALXN1210-301 population had a higher number of PRBC transfusion received within the 12 months before study entry compared to the PRINCE population, and more than one third of the patients enrolled in ALXN1210-301 were Caucasian (38.2%). The ESC advised there was no clear difference in PNH phenotype across different ethnic groups.
	1. After adjusting, the two trial populations were still imbalanced in terms of baseline LDH level, number of PRBC transfusion received in the previous 12 months, as well as race distribution.
	2. Prognostic factors of PNH such as age and race were considered and compared between the two trial populations in the indirect comparison. However, other prognostic factors, including PNH clone size, and the percentages of patients with the history of thrombosis and with bone marrow failure at baseline in each trial, were not considered and compared. These factors raise potential transitivity issues in the indirect comparison.
	3. Overall, the heterogeneities in trial inclusion criteria, definitions of efficacy endpoint, and patient baseline characteristics raised concern about the transitivity of the two studies included in the indirect comparison. Caution should be taken when interpreting the results of the indirect comparison in this context.

Comparative effectiveness

* 1. A summary of the efficacy results of PRINCE is provided in Table 4.

Table 4: Summary of the coprimary and secondary efficacy endpoints of the PRINCE trial

|  | **Pegcetacoplan 1,080 mg SC** **twice weekly****(n = 35)** | **BSC****(n = 18)** |
| --- | --- | --- |
| **Coprimary endpoints** |
| Hb stabilisationa (%) | 30 (85.7) | 0 |
| Differences (95% CI) | 73.1% (57.2, 89.0) |
| p-value | < 0.0001 |
| Change in LDH level from baseline to Week 26 (LS mean [SE], U/L) | -1870.5 (100.97) | -400.1 (313.0) |
| Difference (95% CI) | -1470.4 (-2113.4, -827.3) |
| p-value | < 0.0001 |
| **Secondary endpoints** |
| Hb responsec (%) | 25 (71.4) | 1 (5.6) |
| Differenceb (95% CI) | 54.1% (33.9, 74.3) |
| p-value | < 0.0001 |
| Change in ARC from baseline(LS mean [SE], 109/L) | -123.26 (9.16) | -19.44 (25.21) |
| Differenceb (95% CI) | -103.82 (-158.9, -48.74) |
| p-value | 0.0002 |
| Change in Hb level from baselined(LS mean [SE], g/dL) | 2.94 (0.38) | 0.27 (0.76) |
| Differenceb (95% CI) | 2.67 (0.99, 4.35) |
| p-value | 0.0019 |
| Transfusion avoidancee (%) | 32 (91.4) | 1 (5.6) |
| Differenceb (95% CI) | 72.4 (55.9, 89.0) |
| p-value | < 0.0001 |
| Transfusion required or decrease of Hb > 2 g/dL (%) | 4 (11.4) | 18 (100) |
| Differenceb (95% CI) | -75% (-90.4, -59.7) |
| p-value | < 0.0001 |
| Median (SD) number of PRBC units transfused during the 26-week period | 0 | 3.0 |
| Differenceb (95% CI) | 3.0 (2.0, 4.0) |
| p-value | < 0.0001 |
| Normalisation of Hb level at Week 26f (%) | 16 (45.7) | 0 |
| Differenceb (95% CI) | 36.5% (16.5, 56.4) |
| Normalisation of ARC at Week 26f,g (%) | 21 (60%) | 1 (5.6) |
| Differenceb (95% CI) | 46.3% (25.29, 67.50) |
| Normalisation of LDH level at Week 26f,h (%) | 23 (65.7) | 0 |
| Difference (95% CI) | 55.9% (36.82, 75.02) |
| Change in FACIT-Fatigue Scale score at Week 26 from baselinee (LS mean [SE]) | 7.78 (1.21) | 3.26 (2.11) |
| Differenceb (95% CI) | 4.51 (-0.21, 9.24) |
| p-value | 0.0610 |
| Patients achieved ≥ 3 points improvement at Week 26 (%) | 21 (60) | 2 (11.1) |
| Change in EORTC QLQ-C30 score from baseline (LS mean [SE]) (improvement) | 18.90 (2.91) | -2.85 (5.70) |
| Differenceb (95% CI) | 21.75 (9.35, 34.16) |
| Change in LASA score from baseline (LS mean [SE]) (improvement) | 50.39 (9.06) | -5.39 (17.69) |
| Differenceb (95% CI) | 55.79 (16.83, 94.74) |

Source: Formulated during the evaluation, based on Table 2-31 and Table 2-32, pp62-63 of the submission; pp99-113 of the Pegcetacoplan APL-308 Clinical Study Report.

ARC = absolute reticulocyte count; BSC = best supportive care; CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; Hb = haemoglobin; LASA = Linear Analog Scale Assessment; LDH = lactate dehydrogenase; LS = least square; PRBC = packed red blood cell; SC = subcutaneous; SD = standard deviation; SE = standard error

a Defined as a ≥ 1 g/dL increase in haemoglobin from baseline at Week 26 in the absence of transfusions

b Adjusted difference

c Defined as a ≥ 1 g/dL increase in haemoglobin from baseline at Week 26 in the absence of transfusions

d All values after switching from BSC to pegcetacoplan were set to missing

e Patients who did not have a transfusion but withdrew before Week 26 or escaped from SoC to pegcetacoplan were not considered to have achieved transfusion avoidance

f All values after the intercurrent events including transfusions, treatment escape, discontinuation of study treatment, withdrawal from study, and lost to follow-up, were set to be missing

g Defined as absolute reticulocyte count < 1 x ULN

h Defined as LDH < 1 x ULN (226 U/L)

* 1. Breakthrough haemolysis was the exploratory efficacy endpoint in the PRINCE trial. Two patients (5.7%) randomised to the pegcetacoplan arm (n = 35) experienced breakthrough haemolysis. Among the switch patients (n = 11), no patient experienced breakthrough haemolysis after switching.
	2. Patients treated with pegcetacoplan for 26 weeks demonstrated clinically significant results of stabilised haemoglobin level and lowered LDH level (indicating less haemolysis), compared to patients receiving BSC. Patients with PNH and coexisting aplastic anaemia may have poorer haemoglobin response and stabilisation and higher rates of transfusion. Although there were a higher proportion of patients with aplastic anaemia in the BSC arm of the trial, the magnitude of the benefit of pegcetacoplan is unlikely to be a consequence of the differences in aplastic anaemia across the arms. Due to the open-label design of the study, patient reported outcomes, including the changes in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale score, European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, and Linear Analog Scale Assessment (LASA) score may be subject to bias.
	3. The PRINCE trial did not report on clinically relevant long-term outcomes, and the magnitude of benefit of pegcetacoplan in terms of longer-term or clinically relevant outcomes, including prevention of thromboembolism and improving survival, remains uncertain.

Indirect comparison of pegcetacoplan vs ravulizumab

* 1. Indirect comparisons of pegcetacoplan vs ravulizumab, using unanchored MAIC and unanchored, unadjusted ITC, are presented in Table 5 and Table 6, respectively.

Table 5: Summary of comparative treatment efficacy results (pegcetacoplan vs ravulizumab) in treatment naïve PNH patients using the unanchored MAIC method

| **Trial** | **PRINCE** | **ALXN1210-301** |
| --- | --- | --- |
| Treatment/endpoints | Pegcetacoplan(n = 35) | Ravulizumab(n = 125) |
| Change in LDH level, mean (U/L) | -2,019.23 | -1,255.18 |
|  Difference (95% CI) | -764.05 (-1,093.48, -434.63) |
| p-value | <0.0001 |
| LDH normalisation (%) | 74.94 | 49.00 |
|  Difference (95% CI) | 25.94 (6.40, 45.48) |
| p-value | 0.0093 |
| Haemoglobin stabilisation (%) | 94.35 | 68.00 |
|  Difference (95% CI) | 26.35 (14.83, 37.86) |
| p-value | <0.0001 |
| Transfusion avoidance (%) | 94.35 | 73.60 |
|  Difference (95% CI) | 20.75 (9.55, 31.94) |
| p-value | 0.0003 |
| Breakthrough haemolysis, mean (%) | 0.00 | 4.00 |
|  Difference (95% CI) | -4.00 (-7.44, -0.56) |
| p-value | 0.0225 |
| MAVEs | 0.00 | 1.60 |
|  Difference (95% CI) | -1.60 (-3.80, 0.60) |
| p-value | 0.1540 |
| Change from BL EORTC QLQ-C30 – general health status score, mean | 26.11 | 13.20 |
|  Difference (95% CI) | 12.91 (3.27, 22.56) |
| p-value | 0.0087 |
| Change from BL EORTC QLQ-C30 – physical functioning score, mean | 7.64 | 13.20 |
|  Difference (95% CI) | 5.56 (-11.53, 0.42) |
| p-value | 0.0682 |
| Change from BL EORTC QLQ-C30 – fatigue symptom score, mean | -24.56 | -20.20 |
|  Difference (95% CI) | -4.36 (-16.64, 7.93) |
| p-value | 0.487 |
| Change from BL FACIT – Fatigue score, mean | 9.77 | 7.07 |
|  Difference (95% CI) | 2.70 (-2.38, 7.79) |
| p-value | 0.297 |

Source: Table 2-54, p77 of the submission; Wong et al. (2023)

BL = baseline; CI = confidence interval; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; MAIC = matching-adjusted indirect comparison; MAVEs = major adverse vascular events; U/L = units per litre

Table 6: Summary of comparative treatment efficacy results (pegcetacoplan vs ravulizumab) in treatment naïve PNH patients using the unanchored unadjusted ITC method

| **Trial** | **PRINCE** | **ALXN1210-301** |
| --- | --- | --- |
| Treatment/endpoints | Pegcetacoplan(n = 35) | Ravulizumab(n = 125) |
| Change in LDH level, LS mean (U/L) | -1870.47 | NE |
| Change in LDH level, LS mean (%) | NE | -76.84 |
| LDH normalisation (%) | 23 (65.70) | NR (53.60) |
| Haemoglobin stabilisation, n (%) | 30 (85.70) | NR (68.00) |
| Transfusion avoidance, n (%) | 32 (91.40) | NR (73.60) |
| Breakthrough haemolysis, mean (%) | 2 (5.70) | NR (4.00) |
| Change from BL FACIT – Fatigue score, LS mean | 7.78 | 7.07 |

Source: Table 2-59, p82 of the submission

BL = baseline; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; LS = least square; NE = not estimable; NR = not reported; U/L = units per litre

* 1. In the indirect comparison, efficacy in terms of change in LDH level from baseline, LDH normalisation, haemoglobin stabilisation, and transfusion avoidance numerically favoured pegcetacoplan. However, due to key transitivity concerns, the comparative efficacy of pegcetacoplan and ravulizumab should be interpreted with caution.

Comparative harms

* 1. Table 7 summarises the overall treatment emergent adverse events (TEAEs) in the pegcetacoplan and BSC arms in PRINCE.

**Table 7: Summary of the overall safety of the PRINCE trial**

|  | **Pegcetacoplan (overall)****(n = 46)** | **BSC****(n = 18)****RCP + post-RCP** |
| --- | --- | --- |
|  | **26-week RCP** | **RCP + post-RCP** |
| Any TEAE, n (%) | 33 (71.7) | 35 (76.1) | 12 (66.7) |
| TEAEs by severity, n (%) |
|  Mild  | 16 (34.8) | 12 (26.1) | 7 (38.9) |
|  Moderate  | 13 (28.3) | 17 (37.0) | 3 (16.7) |
|  Severe  | 4 (8.7) | 6 (13.0) | 2 (11.1) |
| SAEs, n (%) | 4 (8.7) | 6 (13.0) | 3 (16.7) |
| TEAEs related to pegcetacoplan, n (%) | 13 (28.3) | 16 (34.8) | NA |
| SAEs related to pegcetacoplan, n (%) | 0 | 0 | NA |
| TEAEs leading to treatment discontinuation, n (%) | 0 | 0 | NA |
| TEAEs leading to death, n (%) | 0 | 1 (2.2) | 1 (5.6) |

Source: formulated during the evaluation; pp137-139 of the Pegcetacoplan APL-308 Clinical Study Report

BSC = best supportive care; NA = not applicable; TEAE = treatment emergent adverse event; RCP = randomised controlled period; SAE = serious adverse event

* 1. In PRINCE, the most commonly reported study drug-related TEAEs during the entire treatment period (i.e., the 26-week RCP + post RCP) included hypokalaemia (6.5%, 3 patients), injection site bruising (4.3%, 2 patients), rash (4.3%, 2 patients), and dizziness (4.3%, 2 patients).
	2. In PRINCE, AEs including (1) injection site reactions (ISRs), (2) infections, including sepsis, (3) haemolytic disorders, (4) thrombosis events, and (5) hypersensitivity events were identified as selected AEs because of the mechanism of action of pegcetacoplan, route of administration, and relevance to PNH. Incidence of selected AEs in the trial are presented in Table 8.

Table 8: Summary of the selected AEs in the PRINCE trial

|  |  |  |
| --- | --- | --- |
| **Selected AEs****n (%)** | **Pegcetacoplan (overall)****(n = 46)** | **BSC****(n = 18)** |
| **26-week RCP** | **RCP + post-RCP** | **RCP + post-RCP** |
| Injection site reactions | 14 (30.4) | 16 (34.8) | NA |
| Infections | 9 (19.6) | 11 (23.9) | 5 (27.8) |
|  Sepsis | 0 | 1 (2.2) | 1 (5.6) |
| Haemolytic disorders | 0 | 3 (5.6) | 0 |
| Thrombosis events | 0 | 0 | 0 |
| Hypersensitivity events | 9 (19.6) | 12 (26.1) | 2 (11.1) |

Source: Table 45, p159 of the Pegcetacoplan APL-308 Clinical Study Report

AE = adverse event; BSC = best supportive care; NA = not applicable; RCP = randomised controlled period

* 1. During the entire treatment period of PRINCE, the most commonly reported TEAEs (≥ 5%) included hypokalaemia and pain in extremity (13% each), dizziness and arthralgia (10.9% each), fever/pyrexia and headache (8.7%), ecchymosis, erythema, musculoskeletal pain, and abdominal pain/upper abdominal pain (6.5% each). Except for hypokalaemia and abdominal pain, other commonly reported TEAEs in the study only occurred in pegcetacoplan treated patients.
	2. In PRINCE, severe TEAEs experienced by pegcetacoplan treated patients included chest pain, neutropenia, febrile neutropenia, anaemia, pancytopenia, septic shock, haemolysis, lymphopenia, hypokalaemia, and bile duct stone. Except for the chest pain (resolved with treatment) and the lymphopenia (not treated and resolved at study completion) that were considered related to the study drug, other severe TEAEs were considered not related to the study drug.
	3. In PRINCE, SAEs experienced by pegcetacoplan treated patients included anaemia, neutropenia, febrile neutropenia, pancytopenia, haemolysis, dermoid cyst, septic shock, and bile duct stone (1 patient each). None of the SAEs reported was considered related to the study drug and none resulted in discontinuation of the study drug. Two patients had SAEs leading to death (one in the pegcetacoplan arm due to septic shock and one in the BSC arm due to respiratory failure and septic shock). Neither death was considered related to pegcetacoplan treatment.
	4. A severe hypokalaemic event occurred in a patient who received pegcetacoplan in the trial, although was not considered to be related to pegcetacoplan by the investigator. In general, safety results from the PRINCE study reflect the known safety profile of pegcetacoplan, however are difficult to interpret due to the small size of the trial, and the limited duration of treatment and follow up.

Indirect comparison of pegcetacoplan vs ravulizumab

* 1. An indirect comparison of incidence of AEs of the pegcetacoplan arm vs ravulizumab arm in the PRINCE and ALXN1210-301 trials is provided in Table 9.

Table 9: Comparative safety of pegcetacoplan versus ravulizumab using the unanchored ITC method

| **Trial** | **PRINCE** | **ALXN1210-301** |
| --- | --- | --- |
| Treatment  | Pegcetacoplan(n = 35) | Ravulizumab(n = 125) |
| Any AEs, n (%) | 33 (71.70) | 110 (88.0) |

Source: Table 2-60, p83 of the submission

AE = adverse event

* 1. Since the two drugs were administered via different routes (SC versus IV) and were dosed with different frequencies (twice weekly versus once every 8 weeks), and the safety profiles reported in PRINCE and ALXN1210-301 were different, the evaluation considered the comparative safety profiles presented in the submission may be unreliable. In PRINCE, injection site reactions and hypokalaemia were the most commonly reported AEs from pegcetacoplan treatment. In ALXN1210-301, headache and upper respiratory tract infection were the most commonly reported AEs from ravulizumab treatment. The numbers of patients included in the comparison were small, and the comparisons were unlikely to be powered to detect a clinically important difference in safety profiles.

Benefits/harms

* 1. A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

* 1. The submission described pegcetacoplan as non-inferior in terms of effectiveness compared to ravulizumab. The ESC considered the claim was likely met but with moderate uncertainty. The evaluation noted although efficacy results in the indirect comparison in terms of change in LDH level from baseline, LDH normalisation, haemoglobin stabilisation, and transfusion avoidance numerically favoured pegcetacoplan, there were considerable concerns relating to the transitivity of the pegcetacoplan study and the ravulizumab study. Furthermore, trial results presented in the submission focused on short-term outcomes, and did not capture longer-term or key patient-relevant outcomes including prevention of thrombosis and improving survival. In March 2022, the PBAC considered the evidence presented for the request of pegcetacoplan listed as the second-line treatment of PNH supported a benefit in short-term haematological outcomes, and noted that no evidence to support non-inferiority in terms of long-term outcomes was presented. The PBAC previously agreed with the ESC that the long-term clinical data for pegcetacoplan was unlikely to be forthcoming for some time and thus the long-term relative benefit to C5is was difficult to measure. The PBAC had also recalled that its recommendation for ravulizumab relied on similar short-term outcomes comparative to eculizumab. Overall, the PBAC previously considered that while uncertain, the claim of non-inferior comparative effectiveness to the known benefits of C5 inhibitor treatment in this population was reasonable (para 7.5, pegcetacoplan PSD, March 2022 PBAC meeting). The PSCR argued there was no plausible clinical explanation as to why the efficacy of pegcetacoplan would differ between lines of therapy.
	2. The ESC acknowledged the difficulty in performing clinical trials in front-line disease when effective therapies were available. The ESC also acknowledged the differences in study design, population and outcome measures increased uncertainty in the comparative effectiveness, noting long-term outcomes have not been measured with pegcetacoplan. However, longer term data was available for eculizumab and ravulizumab as they were historical treatments. Long-term efficacy with these treatments had established complement inhibition as beneficial in PNH, as previously accepted by PBAC when it recommended pegcetacoplan in second-line treatment for PNH.
	3. The submission described pegcetacoplan as non-inferior in terms of safety compared to ravulizumab. The evaluation considered this claim was uncertain and may not be supported by the evidence. Although the safety results from the PRINCE study reflect the known safety profile of pegcetacoplan, it is difficult to interpret due to the small size of the trial, and the limited duration of treatment and follow-up. The two drugs being indirectly compared were administered via different routes and were dosed with different frequencies, and the safety profiles of the two drugs reported in the two trials were different. Therefore, the comparative safety profiles may be unreliable. Furthermore, due to the small numbers of patients included in the comparison, it was unlikely to be powered to detect a clinically important difference in safety profiles.
	4. The ESC noted the PBAC previously considered that the claim of non-inferior comparative safety was uncertain but reasonable in the second-line setting (para 6.54, pegcetacoplan PSD, March 2022 PBAC meeting).
	5. The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable despite some moderate uncertainty.
	6. The PBAC considered that the claim of non-inferior comparative safety was uncertain but reasonable.

Economic analysis

* 1. The submission presented a CMA comparing pegcetacoplan with ravulizumab for the treatment of Ci-naïve patients with PNH, based on the non-inferiority claim.
	2. The submission’s estimate of equi-effective doses over a one-year maintenance treatment period were:
* Pegcetacoplan 1,080 mg x 105.5 injections; and
* Ravulizumab 3,288 mg x 6.5 infusions.
	1. The equi-effective dose of pegcetacoplan was derived from the PRINCE trial, where at the end of the post-RCP, 93.5% (43 out of 46) patients received the dose regimen of 1,080 mg pegcetacoplan twice weekly, and the remaining 6.5% received an escalated dose of 1,080 mg pegcetacoplan once every 3 days. The weighted number of doses per week was therefore estimated to be 2.02,[[15]](#footnote-16) equalling to 105.5[[16]](#footnote-17) doses per year.
	2. The duration of pegcetacoplan treatment in the whole PRINCE study (RCP + post-RCP) was shorter than the time frame of the CMA (median duration of 0.36-0.50 years and mean duration of 0.46-0.67 years in the trial vs. 1 year in the CMA). When the submission of second-line pegcetacoplan was reviewed, the PBAC noted that the proportion of patients in whom the pegcetacoplan dose was escalated increased beyond 16-week study period of the PEGASUS trial. The PBAC considered dosing of pegcetacoplan over the open-label period was more likely to reflect clinical practice (para 7.9, pegcetacoplan PSD, March 2022 PBAC meeting). This is also the case for pegcetacoplan use in the first-line maintenance setting. Among 50 patients enrolled in the PRINCE trial who entered the open-label, long-term extension study (APL2-307), 74% (37/50) patients received pegcetacoplan 1,080 mg twice weekly and 26% (13/50) with an escalated dose of 1,080 mg once every 3 days, based on the assumption that all patients eligible for dose intensification for acute breakthrough haemolysis would instead receive a dose escalation to once every 3 days. The dosing frequency from the extension study is more likely to reflect the circumstance of use of pegcetacoplan as a chronic therapy.
	3. The equi-effective dose of ravulizumab maintenance therapy was sourced from the previous CMA of ravulizumab versus eculizumab and the CMA of second-line pegcetacoplan versus ravulizumab, where the equi-effective dose for ravulizumab was calculated based on weight distributions from the subgroup of Australians in the International PNH registry (ravulizumab PSD, July 2021 PBAC meeting; pegcetacoplan PSD, July 2022 PBAC meeting). The ESC considered this was appropriate.
	4. The ESC considered equi-effective doses over a one-year maintenance treatment period should include the pegcetacoplan OLE study (APL2-307) to capture the higher proportion of patients requiring dose escalation. The revised equi-effective doses were:
* Pegcetacoplan 1,080 mg x 108.88 injections; and
* Ravulizumab 3,288 mg x 6.5 infusions.
	1. Pegcetacoplan is administered via SC infusion with a commercially available syringe system infusion pump. The submission assumed that there would be no administration costs associated with pegcetacoplan therapy as all patients would be self-administering treatment at home. Training for self-administration was costed in other economic evaluations of pegcetacoplan.[[17]](#footnote-18) In addition, there are likely to be some increased MBS costs associated with the administration of some pegcetacoplan provided in healthcare settings, particularly given the frequency of administration (twice weekly or every 3 days), however the extent of this was unknown.
	2. Ravulizumab is administered by IV infusion. The submission estimated the administration costs based on the MBS schedule fee for item 14245 (administration of immunomodulating agent via intravenous infusion for at least 2 hours duration), and the National Efficient Price (NEP) for 2024-2025 period adjusted with the price weight associated with Tier 2 non-admitted hospital services (haematology and immunology). The administration cost assumed in the submission ($317.64) was higher than that in the CMA of ravulizumab versus eculizumab (MBS item 105 schedule fee: $49.75) (ravulizumab PSD, July 2021 PBAC meeting).
	3. Of note, the CMA which formed the basis of PBAC’s positive recommendation for second-line treatment with pegcetacoplan did not include cost offsets associated with the difference in administration route between pegcetacoplan and ravulizumab (Table 1, pegcetacoplan PSD, July 2022 PBAC meeting).
	4. The CMA included the costs of vaccinations against pneumococcal disease and haemophilus influenzae type B infection in patients receiving pegcetacoplan therapy. The resource use and costs associated with vaccinations assumed in the submission were consistent with the CMA in the July 2022 pegcetacoplan (second-line) submission, with MBS fees updated where relevant.
	5. Results of the CMA are presented in Table 10. The CMA was based on the published price for ravulizumab.

Table 10: Results of cost-minimisation analysis

|  |  |  |  |
| --- | --- | --- | --- |
|  | Pegcetacoplan | Ravulizumab | Calculation/explanation |
| Ex-manufacturer price per vial (A) | $4,456.13 | $6,574.12 | PBS listed price for ravulizumab; back-calculated cost-minimised price for pegcetacoplan |
| Vial strength (B) | 1,080 mg | 300 mg | PBS listing |
| Dose per administration (C) | 1,080 mg | 3,288 mg | Equi-effective doses |
| Number of vials required per administration (D) | 1 | 10.96 | = C / B |
| Drug cost per administration (E) | $4,456.13 | $72,052.36 | = A x D |
| Number of administrations per year (F) | 105.49 | 6.50 | Equi-effective doses |
| Drug cost per year (G) | $470,084.12 | $468,340.31 | = E x F |
| Administration cost per IV infusion (H) | – | $317.64 | Weighted administration price based on MBS item 14245a and cost for non-admitted hospital care servicesb |
| Administration cost per year (I) | – | $2,064.66 | = H x F |
| Vaccine cost per patient (J) | $320.85 | – | Vaccinations against pneumococcal disease and HIB infectionc |
| Total cost per year (K) | $470,404.97 | $470,404.97 | = G + I + J |

Source: Table compiled during the evaluation, based on Table 3-4 and Table 3-5, p93 of the submission; “Attachment 3.1 Pegcetacoplan 1L CMA” Excel workbook

HIB = haemophilus influenzae type B; IV = intravenous; MBS = Medicare Benefits Schedule; NEP = National Efficient Price; PBS = Pharmaceutical Benefits Scheme

a MBS item 14245 (schedule fee 111.60): Immunomodulating agent, administration of, by intravenous infusion for at least 2 hours duration - payable once only on the same day and where the agent is provided under section 100 of the Pharmaceutical Benefits Scheme.

b NEP of $6,464, adjusted with price weight for Tier 2 non-admitted hospital code 40.48 – Haematology and immunology (0.0541).

c *S.pneumoniae 13vPCV* administered once over patient lifetime (unit price $85.46 + administration cost $42.85 = $128.31) plus *S.pneumoniae 23PPV* administered twice over patient lifetime ([$38.93 + 42.85] x 2 = $163.56) plus *H. influenzae Type B* administered once over patient’s lifetime ($28.98 + $0.00 = $28.98).

* 1. Of note, the cost-minimised price for pegcetacoplan from the submission’s base case analysis was higher than the proposed published price for pegcetacoplan ($4,456.13 vs. $4,343.86 per 1,080 mg vial). However, this does not reflect the price using the CIC effective ravulizumab price.
	2. Table 11 summarises the sensitivity analyses presented in the submission by changing the proportion of patients receiving more frequent dose of 1,080 mg every 3 days. Additional analyses were performed during the evaluation surrounding the administration costs.

Table 11: Results of sensitivity analyses

|  |  |  |
| --- | --- | --- |
| Analyses | Cost-minimised price for pegcetacoplan per vial | % change from base case |
| Base case | $4,456.13 | – |
| Univariate sensitivity analyses |  |  |
| % receiving pegcetacoplan 1,080 mg once every 3 days (base case: 6.5%, PRINCE trial data) |
| 26%a (extension study data) #1 | $4,317.48 | -3.1% |
| 19.5%b (previous pegcetacoplan second-line submission) #2 | $4,362.92 | -2.1% |
| Administration cost for ravulizumab therapy (base case: $317.64, based on MBS item 14245 and NEP adjusted with price weight for Tier 2 non-admitted hospital code 40.48) |
| $49.75 (MBS item 105) #3 | $4,439.63 | -0.4% |
| $0 #4 | $4,436.56 | -0.4% |
| Administration cost for pegcetacoplan therapy (base case: $0) |
| Inclusion of a clinic appointment with nurse training on use of SC syringe for self-administration (MBS item 82210: $58.85) #5 | $4,455.58 | -0.0% |
| Multivariate sensitivity analyses |  |  |
| #1 AND #4 | $4,298.52 | -3.5% |

Source: Table 3-7, p94 and Table 3-8, p95 of the submission. *Additional analyses performed during the evaluation are presented in italics.*

SC = subcutaneous; MBS = Medicare Benefits Schedule; NEP = National Efficient Price

a The number of doses per year was calculated as (2 x (1 – 26%) + 7 / 3 x 26%) / 7 x 365.25 = 108.88

b The number of doses per year was calculated as (2 x (1 – 19.5%) + 7 / 3 x 19.5%) / 7 x 365.25= 107.75

* 1. The proportion of patients receiving various pegcetacoplan dose regimens had a larger impact on the result than the administration cost. Use of longer-term extension trial data on dosing of pegcetacoplan reduced the cost-minimised price for pegcetacoplan from $4,456.13 per vial to $4,317.48 per vial (-3.1% change). This, in addition to removing cost offsets associated with ravulizumab administration, decreased the pegcetacoplan price further to $4,298.52 per vial (-3.5% change).
	2. If the non-inferiority clam was accepted, the ESC advised the CMA should be consistent with principles previously set when second-line pegcetacoplan was recommended i.e. using the data from the extension period (26% of patients received an escalated dose of pegcetacoplan once every 3 days), additional vaccine costs and removing cost offsets associated with ravulizumab administration.
	3. The pre-PBAC response noted the proposed equi-effective dose for C5i-naïve pegcetacoplan (1,080 mg x 108.9 doses) represented less than a 1% difference compared to the C5i-experienced equi-effective dose (1,080 mg x 107.7 doses). The pre-PBAC response also suggested no change to the current price might be pragmatic given majority of pegcetacoplan use was anticipated to remain among patients switching from C5i therapy, given the established use of ravulizumab and eculizumab in clinical practice, and that dose escalation was unlikely to differ between first and second-line in clinical practice.

Drug cost/patient/year

* 1. The drug cost per patient for pegcetacoplan and ravulizumab are presented in Table 12. Pegcetacoplan drug cost from the CMA was based on the cost-minimised price, which was higher than the proposed public price.

Table 12: **Drug cost per patient for pegcetacoplan and ravulizumab**

|  | Pegcetacoplan | Ravulizumab |
| --- | --- | --- |
| PRINCE trial | CMA | Financial estimates | July 2021 PSD | CMA | Financial estimates |
| Mean dose/ administration | 1,080 mg | 3,288 mga |
| Administrations per week | 2.02b | 0.13 (once every eight weeks) |
| Cost/administration  | $4,345c | $4,456d | $4,345c | $72,059e | $72,052f | $72,059e |
| Cost/patient/week | $8,783 | $9,009 | $8,783 | $9,007 | $8,976 | $9,007 |
| Cost/patient/year | $458,308 | $470,084 | $458,308 | $468,383 | $468,340 | $468,383 |

Source: Table 3-1, p90, Table 3-4, p93 of the submission, “Attachment 4.1 Pegcetacoplan 1L BIM” excel spreadsheet provided with the submission and the ravulizumab PSD, July 2021 PBAC meeting.

CMA = cost-minimisation analysis; HSD = highly specialised drugs; PBAC = Pharmaceutical Benefits Advisory Committee; PI = product information; PSD = public summary document.

Note: A small number of eculizumab scripts was also assumed to be offset in the financial analysis.

a The average maintenance dose of ravulizumab outlined in the ravulizumab PSD (para 6.64, ravulizumab PSD, July 2021 PBAC meeting).

b Based on 94% of patients receiving administrations twice a week and 7% of patients receiving administrations once every 3 days as per the PRINCE trial.

c Based on the proposed published price of pegcetacoplan ($4,344 per 1,080 mg vial), weighted 87% public hospital use (no additional fees) and 13% private hospital use (additional $48.37 in HSD dispensing fees).

d Based on the cost-minimised price (ex-manufacturer price of $4,456 per 1,080 mg vial), not the proposed published price.

e Based on dispensing an average of 2.99 × 1,100 mg vials (costing $24,105 each) or 10.96 × 300 mg vials (costing $6,574 each) per administration, weighted 87% public hospital use (no additional fees) and 13% private hospital use (additional $48.37 in HSD dispensing fees). As the cost per mg is the same for both vial sizes, the resulting cost per administration is the same regardless of the vial size used.

f Based on dispensing an average of 10.96 × 300 mg vials (ex-manufacturer price of $6,574 per vial) per administration.

Estimated PBS usage & financial implications

* 1. This submission was not considered by DUSC. A market share approach was used to estimate the financial impact of listing pegcetacoplan on the PBS. This was reasonable. The key inputs for the financial analysis are presented in Table 13.

Table 13: **Key inputs for financial estimates**

| Data | Value applied and source | Comment |
| --- | --- | --- |
| Number of scripts in a shared market |
| Number of ravulizumab (300 mg vial and 1,100 mg vial scripts) | Observed script utilisation data in 2023, assuming an annual growth of 2.5%. | The growth rate appears to be sourced from a single year of PBS utilisation data (2023). The projected average annual growth rate for overall population was estimated to be 1.2%-1.7% by the ABS. |
| Number of eculizumab scripts |
| Treatment utilisation |
| Pegcetacoplan uptake rate | Ranging from ||||% to ||||% applied to ravulizumab and eculizumab script numbers. Based on the uptake rate in the current pegcetacoplan PBS listing.  | The source of the uptake rate could not be verified during the evaluation however a modest uptake rate may be reasonable given the frequency of infusions associated with pegcetacoplan over ravulizumab and eculizumab. |
| Pegcetacoplan script replacement rate | 2.01:1 for ravulizumab scripts and 0.5:1 for eculizumab scripts. Assuming one script per administration (regardless of vial size for ravulizumab), administered once every eight weeks for ravulizumab and fortnightly for eculizumab and one script every four weeks for pegcetacoplan. | The assumption of one script per administration for ravulizumab may be reasonable as the majority of ravulizumab patients only require one vial size per administration (as per the ravulizumab PSD).a Initial scripts for eculizumab last for four weeks hence the script replacement rate for these script would be 1, however this had a minor impact of the financial analyses. |
| PBS Costs |
| Pegcetacoplan cost per script | $35,134. Based on 8.09 vials being dispensed each script, the weighted average number of vials sufficient for four weeks of treatment as per the PRINCE trial with HSD mark ups. | This cost included 7% of patients receiving an infusion once every 3 days. The cost would increase if the escalated dosing from the OLE study was used (26% of patients receiving an infusion once every 3 days).  |
| Ravulizumab cost per administration. | $72,058. Assumed that each script would dispense the required number of vials to achieve the mean ravulizumab maintenance dose (2.99 for 1,100 mg vials and 10.96 for 300 mg vials) with HSD mark ups. | This was appropriate as it was consistent with CMA and the submission’s assumption of one script was equivalent to one administration. |
| Eculizumab cost per script | $16,934. Based on the number of vials required for the standard maintenance dose of eculizumab (900 mg, 3 × 300 mg vials) with HSD mark ups. | While the cost per script was appropriate for the maintenance eculizumab dose (i.e. continuing scripts), initiating scrips have been underestimated as 8 × 300 mg vials are required for the loading dose, equivalent to the DPMQ of eculizumab initial scripts. However, the financial impact of this was minimal. |
| MBS/NIP costs |
| Administration costs | $80.28 per ravulizumab and eculizumab script replaced. MBS item 14245 with a 80% MBS rebate. | The number of scripts were erroneously double counted. Also, the PBAC previously required the removal of cost offsets for treatment administration in the CMA for the pegcetacoplan listing in second-line PNH, which was also applied to the financial implications (see Table 1, pegcetacoplan PSD, July 2022 PBAC meeting). |
| Vaccination costs | $0. No vaccination costs were included. | The PSCR (p4) noted costs to the NIP have not been considered in the cost and utilisation estimates of any previous PBAC submissions for PNH. The PSCR considered the additional vaccinations will result in minimal additional costs and maintains they should not be considered in the financial estimates. |

Source: Constructed during the evaluation from the “Attachment 4.1 Pegcetacoplan 1L BIM” excel spreadsheet provided with the submission.

ABS = Australian Bureau of Statistics; CMA = cost minimisation analysis; DPMQ = dispensed price for maximum quantity; HSD = highly specialised drugs; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Scheme; PBAC = Pharmaceutical Benefits Advisory Committee; PNH = paroxysmal nocturnal hemoglobinuria; PSD = public summary document.

a Table 16 of the ravulizumab PSD (July 2021 PBAC meeting), indicates that only patients who have a body weight ≥100 kg will require multiple vial sizes (which are listed under different PBS items). Using the mean weight and standard deviation of patients ravulizumab patients in the ALXN1210-PNH-301 and creating a normal distribution, indicates that this only relates to 2% of the ravulizumab population. Hence separate vial sizes and scripts for each patient per administration may be appropriate.[[18]](#footnote-19)

* 1. The estimated extent of use of pegcetacoplan and the financial implications to the PBS per year presented in the submission are outlined in Table 14.

Table 14: **Estimated use and financial implications of listing pegcetacoplan on the PBS**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Description** | **2025** | **2026** | **2027** | **2028** | **2029** | **2030** |
| Projected ravulizumab scriptsa | |||| 1 | |||| 1 | |||| 1 | |||| 1 | |||| 1 | |||| 1 |
| Projected eculizumab scriptsa | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 |
| Pegcetacoplan uptake rate | ||||% | ||||% | ||||% | ||||% | ||||% | ||||% |
| Ravulizumab scripts replaced | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 |
| Eculizumab scripts replaced | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 |
| Pegcetacoplan scriptsb | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 |
| Number of patients treatedi | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 | |||| 2 |
| Cost of pegcetacoplan scripts, less copaymentsc | $|||| 3 | $|||| 3 | $|||| 4 | $|||| 4 | $|||| 4 | $|||| 4 |
| Total cost savings to the PBSd,e | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 |
| Financial impact to the PBS | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 |
| Cost savings to the MBSf | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 |
| Financial impact to the PBS/MBS | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 |
| Net impact to the MBS, revisedg | $|||| 3 | $|||| 3 | $|||| 3 | $|||| 3 | $|||| 3 | $|||| 3 |
| Net impact to the NIP, revisedh | $|||| 3 | $|||| 3 | $|||| 3 | $|||| 3 | $|||| 3 | $|||| 3 |
| Financial impact to the PBS/MBS/NIP, revised | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 | -$|||| 5 |

Source: Constructed during the evaluation from the “Attachment 4.1 Pegcetacoplan 1L BIM” excel spreadsheet provided with the submission.

AEMP = approved ex-manufacturer price; CMA = cost-minimisation analysis; DPMQ = dispensed price for maximum quantity; HSD = highly specialised drugs; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Scheme; PNH = paroxysmal nocturnal hemoglobinuria PSD = public summary document.

a Based on ravulizumab and eculizumab script numbers for PBS item numbers related to PNH in 2023 (PBS items 12884D, 12898W,12841W, 12895Q, 12856P, 12883C, 12901B, 12897T, 12840T, 12877R, 12899X and 12896R), with an annual growth of 2.5%.

b Every replaced ravulizumab script resulted in 2.01 pegcetacoplan scripts and every replaced eculizumab resulted in 0.5 pegcetacoplan scripts. Based on the assumption that one script is required for every eight weeks for ravulizumab (regardless of vial size) and one script every two weeks for eculizumab, both equivalent to the dosing frequency of these drugs and one script every four weeks for pegcetacoplan.

c Cost of each pegcetacoplan script calculated to be $35,322. Based on a weighted average of 8.1 vials dispensed each script, based on the dosing frequency in the PRINCE trial and the proposed AEMP for each vial was $4,344. Weighted 87% public hospital use (no additional fees) and 13% private hospital use (additional $48.37 in HSD dispensing fees) based on ravulizumab utilisation in 2023. Each script was also assumed to include a patient copayment of $25.79, based on ravulizumab utilisation for PNH by beneficiary type in 2023.

d The cost per script for both ravulizumab scripts (1,100 mg vials and 300 mg vial script) was $72,058, based on each script dispensing the required number of vials to achieve the average maintenance dose of 3,288 mg, outlined in the ravulizumab PSD (para 6.56, ravulizumab, PSD, March 2021 PBAC meeting), 10.96 × 1,100 mg vials, costing $24,105 per vial and 2.99 × 300 mg vials, costing $6,574 per vial. Weighted 87% public hospital use (no additional fees) and 13% private hospital use (additional $48.37 in HSD dispensing fees) based on ravulizumab utilisation in 2023. Each script was also assumed to include a patient copayment of $25.79, based on ravulizumab utilisation for PNH by beneficiary type in 2023.

e The cost per script for eculizumab was $16,934, based on dispensing 3 × 300 mg vials, costing $5,640 per vial per script to achieve the standard dose PI dose 900 mg. The cost per script was weighted 75% public hospital use (no additional fees) and 25% private hospital use (additional $48.37 in HSD dispensing fees) based on eculizumab utilisation in 2023. Each script was also assumed to include a patient copayment of $19.61, based on eculizumab utilisation for PNH by beneficiary type in 2023.

f Assuming each replaced ravulizumab and eculizumab script would incur the cost of MBS item MBS item 14245 (full cost $111.60, applied with a 80% MBS rebate). However the number of scripts were erroneously double counted.

g Revised net MBS costs do not include cost offsets due to administration as per financial estimates that were previously accepted by the PBAC (Table 1, pegcetacoplan PSD, July 2022 PBAC meeting). Additional MBS costs ($43 based on MBS item 23, 100% rebate) associated with vaccine administration, two per initiating patient in their first year and one in their fourth year of treatment. Number of initial patients projected based on the number of observed initiating scripts (for ravulizumab and eculizumab in 2023).

h Vaccines per initiating patient include S. pneumoniae 13vPCV, S. pneumoniae 23vPPV and H. influenzae Type B in their first year, costing $85, $39, $29, respectively and a second S. pneumoniae 23vPPV in their fourth year of treatment based on the CMA.

i Number of patients treated was calculated by assuming 13.04 pegcetacoplan scripts per patient per year, with each script supplying 4 weeks of treatment.

*The redacted values correspond to the following ranges:*

*1 500 to < 5,000; 2 < 500; 3 $0 to < $10 million; 4 $10 million to < $20 million; 5 net cost saving*

* 1. The submission estimated a cost saving to the PBS in Year 6 and a total net cost saving over the first six years of listing. This cost saving is driven by the proposed AEMP of pegcetacoplan being lower than the cost-minimised price (see paragraph 6.50).
	2. To calculate the script replacement rate, the submission assumed that each script of ravulizumab and eculizumab was equivalent to one administration. Although different vial sizes (which are listed under different PBS items) are available for ravulizumab, for maintenance doses, only patients who have a body weight of ≥100 kg would require two vial sizes per administration (and hence two scripts) as per the ravulizumab PSD (Table 16, ravulizumab PSD, July 2021 PBAC meeting). A normal distribution using the mean weight and standard deviation of ravulizumab patients enrolled in the ALXN1210-PNH-301 study (the key ravulizumab trial), indicates that this represents only 2% of patients.18 Hence , the submission’s assumption appears reasonable.
	3. The submission estimated cost reductions to the PBS associated with the replaced ravulizumab and eculizumab scripts. While the cost of initiating ravulizumab and eculizumab scripts were not estimated, this did not have a substantial impact on the net financial estimates.
	4. The submission also estimated cost reductions to the MBS based on pegcetacoplan being self-administered and ravulizumab and eculizumab requiring infusion services. The submission estimated that infusions would be required for each ravulizumab and eculizumab script and each administration was assumed to incur the cost of MBS item 14245 (full cost $111.60, applied with a 80% MBS rebate). However, the submission had erroneously double counted the number of replaced ravulizumab and eculizumab scripts. Nonetheless, the PBAC did not previously accept that administration costs would be offset in the previous pegcetacoplan submission for use in the second line (para 7.12, pegcetacoplan PSD, March 2022 PBAC meeting). In line with the pegcetacoplan financial estimates that were accepted by the PBAC, MBS cost offsets associated with reduced administration costs have been removed from the evaluation’s revised estimates (Table 1, pegcetacoplan PSD, July 2022 PBAC meeting).
	5. The submission did not include costs associated with the NIP. This was not reasonable as additional vaccinations are required for pegcetacoplan over ravulizumab and eculizumab (see paragraph 6.41) and these vaccines will be accessed from the NIP. The evaluation has included these costs based on the cost per vaccine and administration outlined in the CMA and the number of initiating patients based on the projected number of initial ravulizumab and eculizumab scripts. The PSCR noted costs to the NIP have not been considered in the cost and utilisation estimates of any previous PBAC submissions for PNH. The PSCR considered the additional vaccinations will result in minimal additional costs and maintains they should not be considered in the financial estimates.
	6. Sensitivity analyses were performed on the financial estimates (Table 15). The only variable which resulted in additional costs to the PBS was varying the proportion of patients who require an infusions once every three days (as opposed to the standard PI dose of twice a week).

Table 15: Results of the key sensitivity analyses performed on the financial impact to the PBS

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Analyses** | **2025** | **2026** | **2027** | **2028** | **2029** | **2030** | **Cost saving** |
| Base case | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | - |
| Annual growth rate of ravulizumab and eculizumab scripts (base case: 2.5%)a |
| 1.2%b | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | Less cost savings |
| 1.7%c | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | Less cost savings |
| Uptake rate of pegcetacoplan (base case: ||||% in Year 1 increasing to ||||% in Year 6)d |
| 2% - 15%e | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | Less cost savings |
| 10% - 50%f | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | More cost savings |
| Proportion of pegcetacoplan patients requiring an infusion once every three days (base case: 6.5%)g |
| 19.5%h | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | Cost incurring |
| 26.0%i | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | $|||| 2 | Cost incurring |
| Cost of ravulizumab and eculizumab initiating scripts (base case: same as continuing scripts) |
| As per ravulizumab PSD and eculizumab PIj | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | -$|||| 1 | Less cost savings |

Source: Constructed during the evaluation from the “Attachment 4.1 Pegcetacoplan 1L BIM” excel spreadsheet provided with the submission.

ABS = Australian Bureau of Statistics; OLE = open label extension; PBS = Pharmaceutical Benefits Scheme; PI = product information; PSD = public summary document.

Note: analyses in italics were performed during the evaluation.

a ABS population growth in the year of 2023.

b Lower bound of the ABS estimate for annual population growth until 2032.

c Upper bound of the ABS estimate for annual population growth until 2032.

d | |%, | |%, | |% and | |% in Year 1, 2, 3 and 4+, respectively.

e 2%, 5%, 8%, 10%, 12% and 15% in Year 1, 2, 3, 4, 5 and 6, respectively.

f 10%, 20%, 30%, 40%, 45% and 50% in Year 1, 2, 3, 4, 5 and 6, respectively.

g Sourced from the PRINCE clinical trial.

h Pegcetacoplan PSD, July 2022 PBAC meeting.

i Sourced from the ALP-307 OLE study.

j Induction dose for eculizumab based on the eculizumab PI (2,400 mg, equivalent to 8 × 300 mg vials) and assuming one initiating eculizumab script was equivalent to one pegcetacoplan script (as these both last four weeks). Mean induction dose of ravulizumab (weight-based) assumed to be 2,491 mg (equivalent to 2.26 × 1,100 mg vials or 8.30 × 300 mg vials) based on the doses outlined in the ravulizumab PSD (para 6.64 and 6.65, ravulizumab PSD, March 2021 PBAC meeting).

*The redacted values correspond to the following ranges:*

*1 net cost saving*

*2 $0 to < $10 million*

Quality Use of Medicines

* 1. The submission outlined the following:
* As pegcetacoplan is self-administered, it would reduce the need for hospital visits for administration
* The Sponsor will provide pegcetacoplan pumps (and other consumable material) for self-administration free of charge to the patient, and
* The sponsor will continue to run a patient support program to facilitate initiation and ongoing management of therapy.

Financial Management – Risk Sharing Arrangements

* 1. The Sponsor proposed no changes to the existing risk-sharing arrangements (RSA) and Deed of Agreement for pegcetacoplan.
1. PBAC Outcome
	1. The PBAC recommended an extension to the existing Section 100 Highly Specialised Drugs Program (HSD) Authority Required (in writing only via post/HPOS upload) listing of pegcetacoplan, to allow for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH) who are either treatment-naïve to complement 5 inhibitors (C5is) or currently treated with a C5i. The PBAC’s recommendation for the extended listing was based on its assessment that the cost-effectiveness of pegcetacoplan would be acceptable if it were cost-minimised against ravulizumab.
	2. The PBAC considered that the equi-effective doses over a one-year maintenance treatment period were pegcetacoplan 1,080 mg x 108.88 injections; and ravulizumab 3,288 mg x 6.5 infusions. The PBAC considered the inclusion of the pegcetacoplan open-label extension (OLE) study (APL2-307) to capture the higher proportion of patients requiring dose escalation was appropriate and consistent with the recommended approach to the dosing for the second-line pegcetacoplan listing (see paragraph 6.37).
	3. The PBAC considered the proposed extended listing for pegcetacoplan was adequately supported by the available clinical evidence (see paragraph 7.10 below) and would provide an alternative treatment option for patients not amenable to IV fusions or for whom regular treatment in a hospital setting was difficult to manage. The PBAC expected C5is would remain the most likely first-line option for patients going forward given the potential severe consequences of non-compliance with the twice-weekly subcutaneous infusion.
	4. The PBAC considered the restriction wording proposed by the Secretariat for the extended PBS listing was appropriate, with criteria for ‘Initial 1’ (complement inhibitor untreated patients) aligned with the C5i PBS listings for PNH, and ‘Initial 2’ (complement inhibitor experienced patients) criteria allowing switching in first-line without requiring Hb <105 g/L, as was currently specified in the current second-line PBS listing.
	5. When switching from a C5i, for the first 4 weeks, pegcetacoplan must be administered in combination with a C5i before commencing pegcetacoplan monotherapy thereafter. The PBAC considered it was appropriate to apply the current ||| |||% rebate for ||| ||| ||| ||| ||| ||| ||| ||| to the initiation of pegcetacoplan in patients switching from a C5i as determined by their treating clinicians regardless of their response to the C5i therapy.
	6. The PBAC noted the request for grandfathering restrictions in the pre-PBAC response (see paragraph 3.5) and considered this was appropriate and for 12 months from date of listing.
	7. The PBAC advised there would need to be flow-on changes to PBS listings for C5is (i.e. eculizumab and ravulizumab) and to iptacopan recommended restrictions (when PBS listed as second-line) to allow for switching between treatments upon intolerance or contraindications. The PBAC also noted pregnancy as a reasonable cause for switching from pegcetacoplan to eculizumab but considered that flow-on changes would not be required given that the current restrictions allow access.
	8. The PBAC accepted ravulizumab was the appropriate comparator. It was noted the PBAC had previously considered ravulizumab would be the C5i most likely to be replaced in clinical practice and hence the appropriate base case comparator for any future cost-minimisation analysis (see paragraph 5.1).
	9. The PBAC noted the comparison between pegcetacoplan and ravulizumab was based on an unanchored matching-adjusted indirect comparison (MAIC) between one randomised controlled trial (RCT) which compared pegcetacoplan to best supportive care (BSC) in treatment naïve PNH patients (PRINCE), and one RCT comparing ravulizumab to eculizumab in treatment naïve patients (ALXN1210-301), The safety of pegcetacoplan and ravulizumab was compared without any adjustments.
	10. The PBAC noted the outcomes of comparative effectiveness from the MAIC in terms of change in lactate dehydrogenase (LDH) level from baseline, LDH normalisation, haemoglobin stabilisation, and transfusion avoidance, numerically favoured pegcetacoplan (see Table 5). The PBAC noted the heterogeneity and transitivity assumptions affected the ability to assess the clinical claim of non-inferior comparative effectiveness based on the MAIC (see paragraphs 6.8 to 6.11), however, the PBAC agreed with the ESC that pegcetacoplan was likely non-inferior to ravulizumab based on this short-term data, despite some moderate uncertainty. The PBAC noted there was no data on long-term efficacy with pegcetacoplan but that it had previously accepted non-inferiority to C5is based on evidence of ongoing stable long-term responses available for eculizumab (see paragraph 6.28 and 6.29).
	11. The PBAC noted that comparative harms would vary by frequency and mode of administration (see paragraph 6.26), with subcutaneous injection site issues with pegcetacoplan, and IV infusion site issues with ravulizumab. The MAIC was not powered to detect a difference in adverse events. Overall, the PBAC considered that the claim of non-inferior comparative safety was uncertain but reasonable.
	12. The PBAC considered a cost-minimisation approach (CMA) was appropriate. The PBAC agreed with the ESC that the CMA should be consistent with the previous CMA for second-line and include data from the OLE period, no cost offsets for ravulizumab infusions, and costs of additional vaccines (see Table 11 and paragraph 6.48). The PBAC noted this resulted in a slightly lower price per vial (approx. 1%) than the current second-line price. The PBAC noted the pre-PBAC response suggested no change to the current price might be pragmatic given majority of pegcetacoplan use was anticipated to remain among patients switching from C5i therapy, given the established use of ravulizumab and eculizumab in clinical practice, and that dose escalation was unlikely to differ between first and second-line in clinical practice. The PBAC considered that overall, the impact to the broader PNH price was likely to be minimal, and it was accepted that the primary role of pegcetacoplan would be for patients not adequately responding to C5is.
	13. The PBAC considered that the structure of the financial estimates was reasonable in capturing the treatment changes between both first and second-line use. The PBAC noted the submission estimated a small savings to Government over 6 years using the proposed published price for pegcetacoplan and published prices for C5is. The PBAC noted the cost savings would be reduced with the inclusion of the escalated dosing from the OLE period, if uptake was lower than predicted (base case: ||| |||% in Year 1 increasing to ||| |||% in Year 6) and with use of effective prices. The PBAC agreed with the submission proposal for no change to the current RSA in place for the complement inhibitors.
	14. The PBAC noted the Product Information for pegcetacoplan included a boxed warning regarding the risk of serious infections caused by encapsulated bacteria, such as Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type B (HIB), with recommendations to vaccinate against these bacteria prior to initiation of pegcetacoplan treatment. The PBAC advised it would be appropriate to extend access on the National Immunisation Program for the vaccinations recommended in the Product Information, not limited to patients with PNH who have an inadequate clinical response or are intolerant to treatment with eculizumab or ravulizumab[[19]](#footnote-20).
	15. The PBAC advised that pegcetacoplan is not suitable for prescribing by nurse practitioners.
	16. The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because pegcetacoplan is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ravulizumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
	17. The PBAC noted that this submission not eligible for an Independent Review as it received a positive recommendation.
	18. The PBAC recommended that the Early Supply Rule should not apply.

**Outcome:**

Recommended

1. Recommended listing
	1. Amend existing listing as follows:

Initial 1 treatment (complement inhibitor untreated patients):

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| PEGCETACOPLAN |
| pegcetacoplan 1.08 g/20 mL injection, 20 mL vial  | NEW (HSD Private)NEW (HSD Public) | 1 | 1 | 0 | Empaveli  |
|  |
| **Category / Program:** [x]  Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS) |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x] Authority Required (in writing only via OPA/post/HPOS upload)  |
| **Authority type:** [x]  Complex Authority Required (CAR) |
| **Prescribing rule level:**  |
| **Caution:**This drug increases the risk of encapsulated bacterial infections.Consult the approved Product Information for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection. |
| **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice:**Complement 5 (C5) inhibitors are defined as eculizumab or ravulizumab |
| **Administrative Advice:**Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use. |
| **Administrative Advice:**Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at [www.servicesaustralia.gov.au](https://www.servicesaustralia.gov.au)Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see [www.servicesaustralia.gov.au/hpos](https://www.servicesaustralia.gov.au/hpos))Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at [www.servicesaustralia.gov.au/hpos](https://www.servicesaustralia.gov.au/hpos)Or mailed to:Services AustraliaComplex DrugsReply Paid 9826HOBART TAS 7001 |
| **Restriction Summary [new1] / Treatment of Concept: [new1A]** |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:** Initial treatment *–* initial 1 (new untreated patient)  |
| **Clinical criteria:** |
| Patient must not have received prior treatment with any of the PBS-subsidised therapies listed for this condition |
| **AND** |
| **Clinical criteria:** |
| Patient must have a diagnosis of PNH established by flow cytometry.  |
| **AND** |
| **Clinical criteria:**  |
| Patient must have PNH granulocyte clone size equal to or greater than 10%  |
| **AND** |
| **Clinical criteria:**  |
| Patient must have a raised lactate dehydrogenase value at least 1.5 times the upper limit of normal. |
| **AND** |
| **Clinical criteria:**  |
| Patient must have experienced a thrombotic/embolic event which required anticoagulant therapy; or |
| Patient must have been transfused with at least 4 units of red blood cells in the last 12 months; or |
| Patient must have chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple haemoglobin measurements not exceeding 70 g/L in the absence of anaemia symptoms; or |
| Patient must have chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple haemoglobin measurements not exceeding 100 g/L in addition to having anaemia symptoms; or |
| Patient must have debilitating shortness of breath/chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded; or |
| Patient must have a history of renal insufficiency, demonstrated by an eGFR less than or equal to 60 mL/min/1.73m2, where causes other than PNH have been excluded; or |
| Patient must have recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded. |
| **AND** |
| **Clinical criteria:**  |
| The treatment must be the sole PBS-subsidised therapy for this condition. |
| **Treatment criteria:** |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details. |
| **Population criteria:** |
| Patient must be at least 18 years of age |
| **Prescribing Instructions:** If the application is submitted through HPOS form upload or mail, it must include:(i) details of the proposed prescription; and(ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| **Prescribing Instructions:** At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information. |
| **Prescribing Instructions:**At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:(i) Haemoglobin (g/L)(ii) Platelets (x109/L)(iii) White Cell Count (x109/L)(iv) Reticulocytes (x109/L)(v) Neutrophils (x109/L)(vi) Granulocyte clone size (%)(vii) Lactate Dehydrogenase (LDH)(viii) the upper limit of normal (ULN) for LDH as quoted by the reporting laboratory(ix) the LDH:ULN ratio (in figures, rounded to one decimal place) |

Initial 2 treatment for complement inhibitor experienced patients:

* 1. Amend the current existing pegcetacoplan listings, item codes: 13196M, 13180Q to Initial 2 treatment (switching from a Complement 5 inhibitor)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| PEGCETACOPLAN |
| pegcetacoplan 1.08 g/20 mL injection, 20 mL vial  | 13180Q(Public) | 1 | 1 | 0 | Empaveli  |
| pegcetacoplan 1.08 g/20 mL injection, 20 mL vial  | 13196M(Private) | 1 | 1 | 0 |
|  |
| **Category / Program:** [x]  Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS) |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x] Authority Required (in writing only via *OPA/*post/HPOS upload)  |
| **Authority type:** [x]  Complex Authority Required (CAR) |
| **Prescribing rule level:**  |
| **Caution:**This drug increases the risk of encapsulated bacterial infections.Consult the approved Product Information for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection. |
| **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice:** Special Pricing Arrangements apply*.* |
| **Administrative Advice:**Complement 5 (C5) inhibitors are defined as eculizumab or ravulizumab |
| **Administrative Advice:**Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use. |
| **Administrative Advice:**Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at [www.servicesaustralia.gov.au](https://www.servicesaustralia.gov.au)*Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see* [*www.servicesaustralia.gov.au/hpos*](https://www.servicesaustralia.gov.au/hpos)*)**Alternatively,* ~~A~~ *a*pplications for authority to prescribe ~~should~~ *can* be submitted online using the form upload facility in Health Professional Online Services (HPOS) at [www.servicesaustralia.gov.au/hpos](https://www.servicesaustralia.gov.au/hpos)Or mailed to:Services AustraliaComplex DrugsReply Paid 9826HOBART TAS 7001 |
| **Restriction Summary edit 13709 / Treatment of Concept: edit 13655**  |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:** Initial treatment *–* ~~(new patient)~~ *initial 2* *(switching from a Complement 5 inhibitor)* |
| **Clinical criteria:** |
| Patient must not have received prior treatment with this drug for this condition |
| **AND** |
| **Clinical criteria:**  |
| Patient must have PNH granulocyte clone size equal to or greater than 10% within the last 3 months |
| **~~AND~~** |
| **~~Clinical criteria:~~** |
| ~~Patient must have experienced an inadequate response to a complement 5 (C5) inhibitor demonstrated by a haemoglobin level of less than 105 g/L; or~~ |
| ~~Patient must be intolerant to C5 inhibitors as determined by the treating physician~~ |
| **AND**  |
| **Clinical criteria:**  |
| Patient must have received treatment with at least one C5 inhibitor for at least 3 months before initiating treatment with this drug unless intolerance of severity necessitating permanent treatment withdrawal had occurred |
| **AND**  |
| **Clinical criteria:**  |
| The treatment must be in combination with one PBS-subsidised C5 inhibitor for a period of 4 weeks during initiation of therapy |
| **Treatment criteria:** |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details. |
| **Population criteria:** |
| Patient must be at least 18 years of age |
| **Prescribing Instructions:** ~~The authority application must be made in writing and must include:~~*If the application is submitted through HPOS form upload or mail, it must include:*~~(1)~~ *(i)* ~~a completed authority prescription form;~~ details of the proposed prescription; and~~(2)~~ *(ii)* a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| **Prescribing Instructions:** At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information. |
| **Prescribing Instructions:**At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:(i) Haemoglobin (g/L)(ii) Platelets (x109/L)(iii) White Cell Count (x109/L)(iv) Reticulocytes (x109/L)(v) Neutrophils (x109/L)(vi) Granulocyte clone size (%)(vii) Lactate Dehydrogenase (LDH)(viii) the upper limit of normal (ULN) for LDH as quoted by the reporting laboratory(ix) the LDH:ULN ratio (in figures, rounded to one decimal place) |

Continuing and grandfather treatment:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| PEGCETACOPLAN |
| pegcetacoplan 1.08 g/20 mL injection, 20 mL vial | 13185Y(Public)  | 1 | 1 | 5 | Empaveli |
| pegcetacoplan 1.08 g/20 mL injection, 20 mL vial | 13197N (Private) | 1 | 1 | 5 |
|  |
| **Category / Program:** [x]  GENERAL - General Schedule (Code GE)  |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x] Authority Required (in writing only via *OPA/*post/HPOS upload)  |
| **Authority type:** [x]  Complex Authority Required (CAR) |
| **Prescribing rule level:**  |
| **Caution:**This drug increases the risk of encapsulated bacterial infections.Consult the approved Product Information for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection. |
| **Administrative Advice:** Special Pricing Arrangements apply*.* |
| **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice:**Complement 5 (C5) inhibitors are defined as eculizumab or ravulizumab |
| **Administrative Advice:**Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use. |
| **Administrative Advice:**Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at [www.servicesaustralia.gov.au](https://www.servicesaustralia.gov.au)*Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see* [*www.servicesaustralia.gov.au/hpos*](https://www.servicesaustralia.gov.au/hpos)*)**Alternatively,* ~~A~~ *a*pplications for authority to prescribe ~~should~~ *can* be submitted online using the form upload facility in Health Professional Online Services (HPOS) at [www.servicesaustralia.gov.au/hpos](https://www.servicesaustralia.gov.au/hpos)Or mailed to:Services AustraliaComplex DrugsReply Paid 9826HOBART TAS 7001 |
| **Restriction Summary edit 13717 / Treatment of Concept: edit 13616**  |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:** First continuing treatment  |
| **Clinical criteria:** |
| ~~Patient must have received PBS-subsidised treatment with this drug for this condition under the 'Initial'~~ *~~(complement inhibitor experienced) or 'Initial' (complement inhibitor inexperienced)~~* ~~or 'Grandfather' treatment restriction~~*Patient must have received PBS-subsidised treatment with this drug for this condition under 'Initial 1'* *(new untreated patient) or 'Initial 2' (switching from a Complement 5 inhibitor).* |
| **AND** |
| **Clinical criteria:** |
| ~~The treatment must not be in combination with a Complement 5 (C5) inhibitor~~*The treatment must be the sole PBS-subsidised therapy for this condition.* |
| **AND** |
| **Treatment criteria:** |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details. |
| **Population criteria:** |
| Patient must be at least 18 years of age |
| **Prescribing Instructions:** ~~The authority application must be made in writing and must include:~~*If the application is submitted through HPOS form upload or mail, it must include:*~~(1)~~ *(i)* ~~a completed authority prescription form;~~ details of the proposed prescription; and~~(2)~~ *(ii)* a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| **Prescribing Instructions:** At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information. A maximum of 5 repeats may be requested. |
| **Prescribing Instructions:**At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:(i) Haemoglobin (g/L)(ii) Platelets (x109/L)(iii) White Cell Count (x109/L)(iv) Reticulocytes (x109/L)(v) Neutrophils (x109/L)(vi) Granulocyte clone size (%)(vii) Lactate Dehydrogenase (LDH)(viii) the upper limit of normal (ULN) for LDH as quoted by the reporting laboratory(ix) the LDH:ULN ratio (in figures, rounded to one decimal place) |
| **Restriction Summary edit 13742 / Treatment of Concept: edit 13743** |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:** Subsequent continuing treatment  |
| **Clinical criteria:** |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition under the 'First Continuing Treatment' ~~or~~*,* 'Return' ~~criteria~~, *or ‘Grandfather’ treatment restrictions* |
| **AND** |
| **Clinical criteria:** |
| Patient must have experienced clinical improvement as a result of treatment with this drug; or |
| Patient must have experienced a stabilisation of the condition as a result of treatment with this drug |
| **AND** |
| **Clinical criteria:** |
| ~~The treatment must not be in combination with a Complement 5 (C5) inhibitor~~*The treatment must be the sole PBS-subsidised therapy for this condition.* |
| **Treatment criteria:** |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details. |
| **Population criteria:** |
| Patient must be at least 18 years of age |
| **Prescribing Instructions:** ~~The authority application must be made in writing and must include:~~*If the application is submitted through HPOS form upload or mail, it must include:*~~(1)~~ *(i)* ~~a completed authority prescription form;~~ details of the proposed prescription; and~~(2)~~ *(ii)* a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| **Prescribing Instructions:** At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information. A maximum of 5 repeats may be requested. |
|  |
| **Restriction Summary [new2] / Treatment of Concept: [new2A]**  |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:** Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather arrangement 1’ (Complement 5 inhibitor inexperienced patients) |
| **Clinical criteria:** |
| Patient must have been receiving non-PBS-subsidised treatment with this drug for this condition prior to [date of listing] |
| **AND** |
| **Clinical criteria:** |
| Patient must have not received treatment for this condition prior to commencing non-PBS subsidised treatment with this drug |
| **AND** |
| **Clinical criteria:** |
| Patient must have a diagnosis of PNH established by flow cytometry prior to commencing non-PBS subsidised treatment with this drug |
| **AND** |
| **Clinical criteria:**  |
| Patient must have a PNH granulocyte clone size equal to or greater than 10% prior to commencing non-PBS subsidised treatment with this drug  |
| **AND** |
| **Clinical criteria:**  |
| Patient must have a raised lactate dehydrogenase value at least 1.5 times the upper limit of normal prior to commencing non-PBS subsidised treatment with this drug |
| **AND** |
| **Clinical criteria:**  |
| Patient must have experienced a thrombotic/embolic event which required anticoagulant therapy prior to commencing non-PBS subsidised treatment with this drug; or |
| Patient must have been transfused with at least 4 units of red blood cells in the last 12 months prior to commencing non-PBS subsidised treatment with this drug; or |
| Patient must have chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple haemoglobin measurements not exceeding 70 g/L in the absence of anaemia symptoms prior to commencing non-PBS subsidised treatment with this drug; or |
| Patient must have chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple haemoglobin measurements not exceeding 100 g/L in addition to having anaemia symptoms prior to commencing non-PBS subsidised treatment with this drug; or |
| Patient must have debilitating shortness of breath/chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded prior to commencing non-PBS subsidised treatment with this drug; or |
| Patient must have a history of renal insufficiency, demonstrated by an eGFR less than or equal to 60 mL/min/1.73m2, where causes other than PNH have been excluded prior to commencing non-PBS subsidised treatment with this drug; or |
| Patient must have recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded prior to commencing non-PBS subsidised treatment with this drug. |
| **AND** |
| **Clinical criteria:**  |
| The treatment must be the sole PBS-subsidised therapy for this condition. |
| **Treatment criteria:** |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details. |
| **Prescribing Instructions:** If the application is submitted through HPOS form upload or mail, it must include:(i) details of the proposed prescription; and(ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| **Prescribing Instructions:**At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:(i) Haemoglobin (g/L)(ii) Platelets (x109/L)(iii) White Cell Count (x109/L)(iv) Reticulocytes (x109/L)(v) Neutrophils (x109/L)(vi) Granulocyte clone size (%)(vii) Lactate Dehydrogenase (LDH)(viii) the upper limit of normal (ULN) for LDH as quoted by the reporting laboratory(ix) the LDH:ULN ratio (in figures, rounded to one decimal place) |
| **Prescribing Instructions:** At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information. A maximum of 5 repeats may be requested. |
| **Prescribing Instructions:** A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a grandfathered patient must qualify under the Subsequent continuing treatment criteria. |
| **Prescribing Instructions:**This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |
|  |
|  | **Restriction Summary [new3] / Treatment of Concept: [new3A]**  |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:** Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather arrangement 2’ (Complement 5 inhibitor experienced patients)  |
| **Clinical criteria:** |
| Patient must have been receiving non-PBS-subsidised treatment with this drug for this condition prior to [date of listing] |
| **AND** |
| **Clinical criteria:**  |
| Patient must have a PNH granulocyte clone size equal to or greater than 10% within the last 3 months prior to commencing non-PBS-subsidised treatment with this drug  |
| **AND**  |
| **Clinical criteria:**  |
| Patient must have received treatment with at least one C5 inhibitor for at least 3 months before initiating non-PBS-subsidised treatment with this drug unless intolerance of severity necessitating permanent treatment withdrawal had occurred |
| **AND**  |
| **Clinical criteria:**  |
| The treatment must be in combination with one PBS-subsidised C5 inhibitor for a period of 4 weeks during initiation of therapy |
| **AND** |
| **Clinical criteria:** |
| The treatment must be the sole PBS-subsidised therapy for this condition. |
| **Treatment criteria:** |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details. |
| **Prescribing Instructions:**At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:(i) Haemoglobin (g/L)(ii) Platelets (x109/L)(iii) White Cell Count (x109/L)(iv) Reticulocytes (x109/L)(v) Neutrophils (x109/L)(vi) Granulocyte clone size (%)(vii) Lactate Dehydrogenase (LDH)(viii) the upper limit of normal (ULN) for LDH as quoted by the reporting laboratory(ix) the LDH:ULN ratio (in figures, rounded to one decimal place) |
| **Prescribing Instructions:** If the application is submitted through HPOS form upload or mail, it must include:(i) details of the proposed prescription; and(ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| **Prescribing Instructions:** At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information. A maximum of 5 repeats may be requested. |
| **Prescribing Instructions:** A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a grandfathered patient must qualify under the Subsequent continuing treatment criteria. |
| **Prescribing Instructions:**This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |

* 1. Flow- on changes to the eculizumab, ravulizumab PBS listings and iptacopan recommended restrictions (to be PBS listed) for paroxysmal nocturnal haemoglobinuria (PNH):
* Amend the treatment phase wording and remove a clinical criterion from eculizumab (12840T, 12896R) and ravulizumab (12898W, 12841W, 12856P, 12901B) listings to allow switching from PBS subsidised pegcetacoplan and iptacopan.

Eculizumab

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT Medicinal Product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of Rpts** | **Available brands** |
| ECULIZUMAB |
| eculizumab 300 mg/ 30 mL injection, 30 mL vial | 12840T (Public)12896R (Private) | 8 | 8 | 0 | Soliris |
|  |
| **Restriction Summary edit 13460 / Treatment of Concept: edit 13459** |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:** *Switching* ~~Return~~ from PBS subsidised pegcetacoplan or iptacopan - induction doses |
| **~~Clinical criteria:~~**  |
| ~~Patient must have received PBS-subsidised treatment with at least one Complement 5 (C5) inhibitor for this condition~~ |
| **~~AND~~** |
| **Clinical criteria:**  |
| Patient must have received PBS-subsidised treatment with either (i) pegcetacoplan, (ii) iptacopan for this condition |
| **AND** |
| **Clinical criteria:**  |
| Patient must have developed resistance or intolerance to either (i) pegcetacoplan, (ii) iptacopan |
| **AND** |
| **Clinical criteria:**  |
| The treatment must be the sole PBS-subsidised therapy for this condition. |
| **Treatment criteria:**  |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient’s drug treatment details |

Ravulizumab

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT Medicinal Product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of Rpts** | **Available brands** |
| RAVULIZUMAB |
| ravulizumab 300 mg/3 mL injection, 3 mL vial  | 12898W (Public)12841W (Private) | 1 | 1 | 0 | Ultomiris |
| ravulizumab 1.1 g/11 mL injection, 11 mL vial  | 12856P (Public)12901B (Private) | 1 | 1 | 0 |
|  |
| **Restriction Summary edit 14533 / Treatment of Concept: edit 14477** |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:**  *Switching* ~~Return~~from PBS subsidised pegcetacoplan or iptacopan - induction doses |
| **~~Clinical criteria:~~**  |
| ~~Patient must have received PBS-subsidised treatment with at least one Complement 5 (C5) inhibitor~~~~for this condition~~ |
| **~~AND~~** |
| **Clinical criteria:**  |
| Patient must have received PBS-subsidised treatment with either (i) pegcetacoplan, (ii) iptacopan for this condition |
| **AND** |
| **Clinical criteria:**  |
| Patient must have developed resistance or intolerance to either (i) pegcetacoplan, (ii) iptacopan |
| **AND** |
| **Clinical criteria:**  |
| The treatment must be the sole PBS-subsidised therapy for this condition. |
| **Treatment criteria:**  |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient’s drug treatment details |

* 1. Amend a clinical criterion in the iptacopan restrictions (to be PBS listed) to allow switching from PBS subsidised pegcetacoplan at any line of therapy to iptacopan.

Iptacopan

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT Medicinal Product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of Rpts** | **Available brands** |
| IPTACOPAN |
| iptacopan 200 mg capsule, 56 | NEW | 1 | 56 | 5 | Fabhalta |
|  |
| **Restriction Summary [new4] / Treatment of Concept: [new4A]** |
| **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) |
| **Treatment Phase:** Initial treatment (new patient) |
| **Clinical criteria:**  |
| Patient must not have received prior treatment with this drug for this condition, |
| **AND** |
| **Clinical criteria:**  |
| Patient must have PNH granulocyte clone size equal to or greater than 10% within the last 3 months, |
| **AND** |
| **Clinical criteria:**  |
| ~~Patient must have experienced an inadequate response to a Complement 5 (C5) inhibitor demonstrated by a haemoglobin level of less than 105 g/L; OR~~ *Patient must have experienced an inadequate response/intolerance to* *either: (i) Complement (C5) inhibitor, (ii) pegcetacoplan.* |
| ~~Patient must be intolerant to C5 inhibitors as determined by the treating physician~~ |
| **AND** |
| **Clinical criteria:**  |
| Patient must have received treatment with at least one ~~C5~~ *Complement* inhibitor for at least 3 months before initiating treatment with this drug unless intolerance of severity necessitating permanent treatment withdrawal had occurred. |
| **AND** |
| **Clinical criteria:**  |
| The treatment must be the sole PBS-subsidised therapy for this condition. |
| **Treatment criteria:**  |
| Must be treated by a haematologist; or |
| Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient’s drug treatment details |

***These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor’s Comment

Sobi welcomes the PBAC’s positive recommendation, which supports earlier access to pegcetacoplan for Australian PNH patients.

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4. Nishimori, H., Nakazawa, H., Tamura, S., Uchida, T., Usuki, K., Szamosi, J., de Latour, R. P., Röth, A., & Panse, J. (2025). Efficacy, Safety, and Quality of Life of Pegcetacoplan in Japanese Patients with Paroxysmal Nocturnal Hemoglobinuria Treated within the Phase 3 PEGASUS Trial. *Acta Haematol*, *148*(1), 22-35. [↑](#footnote-ref-5)
5. Dingli, D., Maciejewski, J. P., Larratt, L., Go, R. S., Höchsmann, B., Zu, K., ... & Kulagin, A. D. (2023). Relationship of paroxysmal nocturnal hemoglobinuria (PNH) granulocyte clone size to disease burden and risk of major vascular events in untreated patients: results from the International PNH Registry. *Annals of hematology*, *102*(7), 1637-1644. [↑](#footnote-ref-6)
6. Lee, J. W., Jang, J. H., Kim, J. S., Yoon, S. S., Lee, J. H., Kim, Y. K., ... & Sohn, S. K. (2013). Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry. *International journal of hematology*, *97*, 749-757. [↑](#footnote-ref-7)
7. Schrezenmeier, H., Röth, A., Araten, D. J., Kanakura, Y., Larratt, L., Shammo, J. M., ... & Maciejewski, J. P. (2020). Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. *Annals of hematology*, *99*, 1505-1514. [↑](#footnote-ref-8)
8. R. J. Kelly et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood. 2011: 117(25); 6786-6792. [↑](#footnote-ref-9)
9. L. A. McNamara et al. High Risk for Invasive Meningococcal Disease Among Patients Receiving Eculizumab (Soliris) Despite Receipt of Meningococcal Vaccine. The Morbidity and Mortality Weekly Report. 2017: 66(27); 734-737. [↑](#footnote-ref-10)
10. D. Dingli et al. The burden of illness in patients with paroxysmal nocturnal hemoglobinuria receiving treatment with the C5-inhibitors eculizumab or ravulizumab: results from a US patient survey. Annals of Hematology. 2022: 101(2); 251-263. [↑](#footnote-ref-11)
11. J. Panse. Paroxysmal nocturnal hemoglobinuria: Where we stand. American Journal of Hematology. 2023: 98 (S4); S20-S32. [↑](#footnote-ref-12)
12. G. F. Gerber & R. A. Brodsky. Pegcetacoplan for paroxysmal nocturnal hemoglobinuria. Blood. 2022: 139(23); 3361-3365. [↑](#footnote-ref-13)
13. Panse et al. PLoS One 2024 2. Cella et al. Cancer2002. [↑](#footnote-ref-14)
14. Wong R, Fishman J, et al. Comparative effectiveness of pegcetacoplan versus ravulizumab and eculizumab in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria: A matching-adjusted indirect comparison. Advances in Therapy. 2023;40(4):1571-89. [↑](#footnote-ref-15)
15. = 93.5% x 2 + 6.5% x (7 / 3) [↑](#footnote-ref-16)
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19. https://www.legislation.gov.au/F2014L01255/latest/text [↑](#footnote-ref-20)