5.07 IPTACOPAN,  
Capsule 200 mg,  
Fabhalta®,  
NOVARTIS PHARMACEUTICALS AUSTRALIA PTY LIMITED.

1. Purpose of submission
   1. The Category 1 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing of iptacopan for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH) who have inadequate clinical response to C5 inhibitor treatment.
   2. Listing was requested on the basis of a cost-minimisation approach versus pegcetacoplan.

Table 1: Key components of the clinical issue addressed in the submission

| Component | Description |
| --- | --- |
| Population | Patients with PNH with residual anaemia despite treatment with a C5 inhibitor. |
| Intervention | Iptacopan 200 mg orally twice a day. |
| Comparator | Pegcetacoplan 1,080 mg administered by subcutaneous infusion twice weekly a |
| Outcomes | Change from baseline in haemoglobin levels, transfusion avoidance, change from baseline in LDH, change from baseline in absolute reticulocyte count, change from baseline in FACIT-Fatigue score, adverse events. |
| Clinical claim | In patients with persistent anaemia despite C5 inhibitor therapy, iptacopan is non-inferior in terms of effectiveness and safety compared to pegcetacoplan. |

Source: Table 1-1, of the submission.

Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria.

a Patients initiated pegcetacoplan at a dose of 1,080 mg twice a week but may have increased to 1,080 mg every third day if they did not respond sufficiently to treatment.

1. Background

Registration status

* 1. ***TGA status at time of PBAC advice****:* The submission was made under the TGA/PBAC Parallel Process. At the time of the evaluation for PBAC consideration, the second round clinical evaluation report was available. The TGA delegate’s overview was provided on 3 June 2024 with the TGA delegate requesting independent expert advice rather than consideration at the 7 June 2024 ACM meeting.
  2. The proposed indication for iptacopan is for the treatment of adult patients with PNH.
  3. The second round TGA clinical evaluator recommended approval of iptacopan for the treatment of adult patients with PNH who have been previously treated with a C5 inhibitor and experienced an inadequate response, based on the favourable benefit-risk balance in this population. The evaluator noted that there are residual uncertainties with regard to use of iptacopan for the treatment of adults with PNH as first-line therapy, due to the lack of controlled clinical trial data in this population.
  4. The Delegate was inclined to approve registration. One of the issues the Delegate identified for independent expert advice was as follows:

“The clinical evaluator has recommended restricting the indication to patients who have previously had a C5 inhibitor, due to the lack of comparative data for patients who are anti-C5 antibody naïve. However, the delegate is of the view that the magnitude of benefit seen in the APPOINT-PNH study [single arm trial of in patients naive to complement inhibitor therapy] is sufficient evidence to support an unrestricted indication. The FDA and EMA have not restricted the indication, but the EMA indication does specify patients with ‘haemolytic anaemia.’”

* 1. Iptacopan was approved by the FDA on 5 December 2023 for the treatment of adults with PNH. Iptacopan received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 21 March 2024, for use as monotherapy in the treatment of adult patients with PNH who have haemolytic anaemia.

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

1. Requested listing
   1. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | | **PBS item code** | **Dispensed Price for Max. Qty** | **Max. qty packs** | **Max. qty units** | **№.of**  **Rpts** | **Available brands** |
| Iptacopan | | | | | | | | |
| Iptacopan 200 mg capsule, 56 | | | NEW | Public hospital: $38,657.22  Private hospital: $38,705.59 | 1 | 56 | ~~0~~ *5* | Fabhalta |
|  | | | | | | | | |
| **Restriction Summary [new] / Treatment of Concept: [new]** | | | | | | | | |
|  | | **Category / Program:** ~~Section 100~~ *General schedule (code: GE)* | | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | | |
| **Restriction type:** Authority Required – In Writing/HPOS | | | | | | |
| 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:***  *Complement 5 (C5) inhibitors are defined as eculizumab or ravulizumab* | | | | | | |
|  | ***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*  *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos*  *Or mailed to:*  *Services Australia*  *Complex Drugs*  *Reply Paid 9826*  *HOBART TAS 7001* | | | | | | |
|  | ***Administrative Advice:***  *No increase in the maximum quantity or number of units may be authorised.* | | | | | | |
|  | ***Administrative Advice:***  *No increase in the maximum number of repeats may be authorised.* | | | | | | |
|  | | **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 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 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:  (1) a completed authority prescription form; and  (2) 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 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) | | | | | | |
|  | | | | | | | | |
|  | | **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) | | | | | | |
|  | | **Treatment Phase:** Return from PBS-subsidised eculizumab post pregnancy ~~or from PBS-subsidised Complement 5 (C5) inhibitor for reasons other than post pregnancy.~~ | | | | | | |
|  | | **Clinical criteria:** | | | | | | |
|  | | Patient must have received prior PBS-subsidised treatment with this drug for this condition, | | | | | | |
|  | | **AND** | | | | | | |
|  | | **Clinical criteria:** | | | | | | |
|  | | Patient must have received prior PBS-subsidised treatment with eculizumab through the 'Initial treatment - Initial 3 (switching from PBS-subsidised ***pegcetacoplan or* iptacopan** for pregnancy (induction doses)' criteria; ~~OR~~ | | | | | | |
|  | | ~~Patient must have received prior PBS-subsidised treatment with at least one C5 inhibitor and returning to iptacopan treatment for reasons other than post pregnancy~~, | | | | | | |
|  | | **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 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:  (1) a completed authority prescription form; and  (2) 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 Instruction****:*  *For the purposes of family planning, patient may qualify under this treatment phase more than once. ~~To return to iptacopan treatment for reasons other than post pregnancy, patient may qualify under this treatment phase once only in any 12 consecutive months. Where long-term continuing PBS-subsidised treatment with iptacopan is planned, a 'Returning' patient must proceed under the ‘Continuing Treatment' criteria of iptacopan. .~~* | | | | | | |

* 1. The submission noted that pegcetacoplan is subject to a special pricing arrangement and that the effective price of pegcetacoplan is unknown. Prices included in the submission were based on the cost-minimised price of iptacopan to the published prices of pegcetacoplan.
  2. The proposed restriction is narrower than the proposed TGA indication, which also includes treatment of patients with no prior C5 inhibitor use.
  3. The proposed clinical criteria, treatment criteria, population criteria, and prescribing instructions included in the initial treatment restriction are consistent with the pegcetacoplan PBS listing, apart from the requirement that the initial 4 weeks of treatment must be in combination with a PBS-subsidised C5 inhibitor. The proposed separation of treatment phases to match the pegcetacoplan restriction may not be necessary given that combination treatment with a C5 inhibitor during the initial 4 weeks of iptacopan treatment is not required.
  4. The pegcetacoplan restriction includes the following cautions which are not included in the proposed restriction, but may also be relevant to iptacopan:

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.

The Economic Sub-Committee (ESC) advised that these cautions should also be added to the proposed iptacopan restriction. The pre-PBAC response agreed with the ESC that these cautions be added to the proposed iptacopan restriction.

* 1. While the proposed clinical criteria relating to inadequate response to a C5 inhibitor is consistent with the pegcetacoplan PBS listing, the specified haemoglobin level of less than 105 g/L differs from the haemoglobin level specified in the key trial (APPLY-PNH; haemoglobin less than 100 g/L). The ESC considered it was appropriate for the clinical criteria to remain consistent with the pegcetacoplan PBS listing.
  2. The PBS listings for eculizumab and ravulizumab allow patients treated with pegcetacoplan to reinitiate treatment with eculizumab or ravulizumab if they have developed resistance or intolerance to pegcetacoplan. Flow on changes may be required to also allow patients who develop resistance or intolerance to iptacopan to reinitiate treatment with eculizumab or ravulizumab. This would also provide a path for patients who develop resistance or intolerance to iptacopan to switch from iptacopan to pegcetacoplan (noting that patients wishing to switch from iptacopan to pegcetacoplan are likely to require bridging therapy with a C5 inhibitor in the first 4 weeks). The pre-PBAC response stated that all reports to date of patients in clinical trials who needed to discontinue iptacopan have involved them switching back to a C5 inhibitor.
  3. The submission requested grandfather provisions to allow patients enrolled in the sponsor’s patient familiarisation and compassionate access programs to receive PBS treatment with iptacopan treatment if it is PBS listed. Estimates of the expected number of grandfathered patients were not presented in the submission.

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

1. Population and disease
   1. PNH is a rare, chronic disorder characterised by haemolysis, bone marrow failure and thrombosis. It is caused by acquired mutations in the phosphatidylinositol glycan A (PIGA) gene in haematopoietic stem cells. Red blood cells carrying the mutations lack CD55 and CD59 regulatory proteins on their cell surface, rendering them susceptible to complement-mediated haemolysis.
   2. Although PNH can affect patients of all ages, it primarily affects adults, and is most frequently diagnosed between the ages of 30 and 40 years. It occurs equally in males and females. Signs and symptoms of PNH include fatigue, shortness of breath, abdominal pain, haemoglobinuria, bone marrow suppression, renal impairment, erectile dysfunction, pulmonary hypertension, and thrombosis. Patients with untreated PNH have a high risk of premature death, predominantly due to the occurrence of life-threatening thrombotic events.
   3. Prior to the availability of C5 inhibitors, treatment was primarily supportive, comprising blood transfusions, erythropoiesis-stimulating agents, anticoagulants to treat thromboses, and corticosteroids. While there is potential for cure with allogeneic stem cell transplantation, it is generally reserved for patients with severe bone marrow failure, due to the high level of associated morbidity and mortality. The availability of C5 inhibitors has reduced the incidence of thrombotic complications associated with intravascular haemolysis and improved the life expectancy of patients with PNH. However, despite treatment with a C5 inhibitor, a number of patients experience persistent anaemia due to breakthrough haemolysis and/or extravascular haemolysis necessitating ongoing blood transfusions.
   4. The submission positioned iptacopan as an alternative treatment to pegcetacoplan, eculizumab and ravulizumab, among adult patients with PNH who have residual anaemia following treatment with a C5 inhibitor (eculizumab or ravulizumab).
   5. Iptacopan acts proximally in the alternative complement pathway to inhibit Factor B, a protease involved in the regulation of C3 convertase activity. Inhibition of Factor B leads to a reduction in the production of C3b, and a consequent reduction in the downstream generation of C5. Due to effects on both C3 and C5 in the complement cascade, iptacopan decreases complement-mediated intravascular haemolysis as well as extravascular haemolysis.

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

1. Comparator
   1. The submission nominated pegcetacoplan as the main comparator. The main argument provided in support of this nomination was that the requested place in therapy for iptacopan is the same as for pegcetacoplan (adult patients with PNH who have inadequate response or intolerance to a C5 inhibitor). The ESC consideredpegcetacoplan is an appropriate main comparator.
   2. The submission did not identify any other comparators. Danicopan, a complement Factor D inhibitor, is currently being assessed by the TGA for the treatment of PNH and is a potential near-market comparator. The proposed TGA indication is as an add-on (to C5 inhibitor therapy) for the treatment of the signs or symptoms of extravascular haemolysis in adult patients with PNH.

*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 clinicians discussed the mechanism of action of iptacopan and how the drug would likely be used in practice based on the benefits reported in clinical trials. The clinicians highlighted the potential advantages of an oral therapy compared to the currently available intravenous or subcutaneous treatments, particularly in patients with needle phobia or with poor venous access. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

* 1. The PBAC noted and welcomed the input from health care professionals (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with iptacopan including improved haemoglobin levels and symptom control along with a reduction in the need for transfusion compared to inadequate response with a C5 inhibitor. The comments highlighted both potential benefits and concerns arising from iptacopan being an oral therapy. Benefits included the ease of administration compared to intravenous or subcutaneous treatments and an increased ability for travel due to greater ease of access. Concerns included the potential for non-adherence due to the need for more frequent administration of oral therapy and hence the potential for breakthrough haemolysis along with the need for strategies for when patients are unable to take oral therapy (such as emergency surgery).

Clinical trial

* 1. No head-to-head trials comparing iptacopan and pegcetacoplan were identified in the literature search. The clinical claim was based on the following indirect comparisons of iptacopan versus pegcetacoplan:

A Bucher method indirect comparison of iptacopan (APPLY-PNH) versus pegcetacoplan (PEGASUS) using the trial control arms (APPLY-PNH: eculizumab or ravulizumab; PEGASUS: eculizumab) as the common reference.

An anchored MAIC of iptacopan (APPLY-PNH) versus pegcetacoplan (PEGASUS) using the trial control arms (APPLY-PNH: eculizumab or ravulizumab; PEGASUS: eculizumab) as the common reference.

An unanchored MAIC of iptacopan (APPLY-PNH) versus pegcetacoplan (PEGASUS).

* 1. The submission excluded the APPOINT-PNH study, a single arm study assessing the efficacy and safety of iptacopan for the first-line treatment of patients with PNH, on the basis that the study population is outside of the proposed PBS population. While this exclusion was reasonable, results from the APPOINT-PNH study were submitted as part of the TGA application to support a broader marketing indication that includes first-line treatment of patients with iptacopan.
  2. Details of the 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 |
| --- | --- | --- |
| APPLY-PNH (NCT04558918) | A randomized, multicenter, active-comparator controlled, open-label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult patients with PNH and residual anemia, despite treatment with an intravenous anti-C5 antibody. | Final clinical study report, November 2023.Interim clinical study report, March 2023. |
| de Latour RP, Roth A, Kulasekararaj AG, Han B, et al. Oral iptacopan monotherapy in paroxysmal nocturnal hemoglobinuria. | *NEJM* 2024; 390(11): 994-1008. |
| PEGASUS (NCT03500549) | Panse J, Wilson K, Fishman J, Wojciechowski P, et al. Fatigue and health-related quality of life in paroxysmal nocturnal haemoglobinuria: A post hoc analysis of the pegcetacoplan PEGASUS trial data. | *European Journal of Haematology* 2023; 111(1): 72-83. |
| Cella D, Sarda SP, Hsieh R, Fishman J, et al. Changes in hemoglobin and clinical outcomes drive improvements in fatigue, quality of life, and physical function in patients with paroxysmal nocturnal hemoglobinuria: post hoc analyses from the phase III PEGASUS study. | *Annals of Hematology* 2022; 101(9): 1905-1914. |
| Desai D, Fishman J, Zhang X. MDS-136 rapid time to a clinically meaningful response in FACIT-Fatigue scores with pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria: a Kaplan-Meier analysis from the PEGASUS Trial. | *Clinical Lymphoma, Myeloma and Leukemia* 2022; 22(Supplement 2): S306. |
| Hillmen P, Szer J, Weitz I, Roth A, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. | *NEJM* 2021; 384(11): 1028-1037. |
| de Latour RP, Szer J, Weitz IC, Roth A et al. Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PEGASUS): 48-week follow-up of a randomised, open-label, phase 3, active-comparator, controlled trial. | *Lancet Haematol.* 2022; 9(9): e648-e659. |

Source: Table 2-6, of the submission.

Selected publications relating to conference abstracts omitted.

* 1. The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcomes |
| --- | --- | --- | --- | --- | --- |
| Iptacopan versus C5 inhibitor | | | | | |
| APPLY-PNH | 97 | MC, OL trial with a 24-week active-controlled randomised phase (iptacopan vs C5 inhibitor) and a 24-week extension phase (iptacopan). | High | Adults with PNH, clone size ≥10%, stable C5 inhibitor regimen for ≥6 months, mean Hb <10.0 g/dL; excluded patients with evidence of bone marrow failure. | * Increase from baseline in Hb ≥2 g/dL (co‑primary) * Achievement of Hb ≥12 g/dL (co‑primary) * Absence of blood transfusions * Change from baseline in haemoglobin level * Change from baseline in ARC * Change from baseline in LDH * Occurrences of breakthrough haemolysis * Occurrence of major adverse vascular events * Change from baseline in FACIT-Fatigue score * Adverse events |
| **Pegcetacoplan versus eculizumab** | | | | | |
| PEGASUS | 80 | MC, OL trial with a 4‑week run-in phase (pegcetacoplan + eculizumab), a 16‑week randomised phase (pegcetacoplan vs eculizumab), and a 32-week extension phase (pegcetacoplan). | High | Adults with PNH, stable eculizumab regimen for ≥3 months chemo, Hb <10.5 g/dL, ARC >1.0 x upper limit of normal, platelet count >30,000/mm3, ANC >500/mm3, BMI <35.0 kg/m2. | * Change from baseline in haemoglobin level * Change from baseline in ARC * Change from baseline in LDH * Units of packed red blood cells transfused * Incidence of thromboembolic events * Change from baseline in FACIT-Fatigue score * Change from baseline in LASA score * Adverse events |

Source: Table 2-10,; Table 2-12,; Section 2.4.3, of the submission.

Abbreviations: ANC, absolute neutrophil count; ARC, absolute reticulocyte count; BMI, body mass index; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LASA, Linear Analogue Assessment Scale; LDH, lactate dehydrogenase; MC, multi-centre; OL, open-label; PNH, paroxysmal nocturnal haemoglobinuria.

* 1. The APPLY-PNH and PEGASUS trials each had a high risk of bias. As the trials were open label, investigators, patients and study personnel were not blinded to treatment assignment. Knowledge of the treatment assignment may have influenced the management of patients and/or the reporting of subjective outcomes (such as the FACIT-Fatigue score) in the trials. The ESC considered that although the APPLY-PNH and PEGUSUS trials were associated with a high risk of bias, the majority of outcomes were objective and standard in PNH.The indirect comparisons presented in the submission were conducted post hoc and were also associated with a high risk of bias.
  2. The inclusion of a 4-week run-in period in the PEGASUS trial, during which patients received treatment with pegcetacoplan in addition to their prior regimen of eculizumab, was a key difference between the APPLY-PNH and PEGASUS trials. The submission noted that there were large differences in some of the outcomes between the control arms of the trials, and suggested that the differences may be due to the cessation of pegcetacoplan in the eculizumab arm at the end of the 4-week run-in period:

A lower proportion of patients in the C5 inhibitor arm of the APPLY-PNH trial required a blood transfusion compared to the eculizumab arm of the PEGASUS trial (60% versus 85%).

Patients in the C5 inhibitor arm of the APPLY-PNH trial experienced a smaller reduction in mean haemoglobin compared to the eculizumab arm of the PEGASUS trial (-0.06 g/dL versus -1.47 g/dL).

Patients in the C5 inhibitor arm of the APPLY-PNH trial experienced a smaller increase from baseline in absolute reticulocyte count compared to the eculizumab arm of the PEGASUS trial (0.34 x109/L versus 28 x109/L).

A lower proportion of patients in the C5 inhibitor arm of the APPLY-PNH trial experienced breakthrough haemolysis (17.1% versus 23.1%).

* 1. There were differences between treatment arms of the APPLY-PNH trial, including differences in median age (53 years versus 45 years in the iptacopan and C5 inhibitor arms, respectively), mean disease duration (11.9 years versus 13.6 years), mean duration of C5 inhibitor treatment (3.8 years versus 4.2 years), mean platelet count (160.2 x 109/L versus 147.3 x 109/L), mean baseline FACIT-Fatigue total score (34.7 versus 30.8), and the proportion with a history of at least one major adverse vascular event (19.4% versus 25.7%). These differences may have impacted the treatment outcomes reported for the trial.
  2. There were differences between treatment arms of the PEGASUS trial in mean age (50.2 years versus 47.3 years in the pegcetacoplan and eculizumab arms, respectively), proportion of female patients (66% versus 56%), proportion with White race (59% versus 64%), median disease duration (6.0 years versus 9.7 years), duration of eculizumab treatment (4.4 years versus 3.4 years), the baseline lactate dehydrogenase level (257.5 U/L versus 308.6 U/L), proportion with ≥4 transfusions in the prior 12 months (51% versus 59%), mean platelet count (166.6 x 109/L versus 146.9 x 109/L), and the proportion with a history of aplastic anaemia (27% versus 23%). These differences may have impacted the treatment outcomes reported for the trial.
  3. Based on a comparison of baseline patient characteristics between the APPLY-PNH and PEGASUS trials, the APPLY-PNH trial included a higher proportion of female patients (69.4% and 68.6% in the iptacopan and C5 inhibitor arms, respectively, versus 66% and 56% in the pegcetacoplan and eculizumab arms, respectively), a higher proportion of patients with White race (77.4% and 74.3% versus 59% and 64%), a longer median disease duration (9.0 years and 11.6 years versus 6.0 years and 9.7 years), a shorter median duration of C5 inhibitor treatment (2.6 years and 2.7 years versus 4.4 years and 3.4 years), a higher mean haemoglobin (8.9 g/dL and 8.9 g/dL versus 8.7 g/dL and 8.7 g/dL), a lower proportion of patients with a transfusion in the prior 12 months (60% and 63% versus 76% and 74%), a lower proportion with ≥4 transfusions in the prior 12 months (26.8% overall versus 51% and 59%), a lower mean absolute reticulocyte count (193.2 x109/L and 190.6 x109/L versus 217.5 x109/L and 216.2 x109/L) and a lower proportion of patients with aplastic anaemia (14.5% and 14.3% versus 27% and 23%). The ESC noted the differences in baseline patient characteristics between the APPLY-PNH and PEGASUS trials. However, the ESC considered that, with the exception of the proportion of patients with aplastic anaemia, the differences in patient characteristics between the trials were not clinically important in the context of PNH.
  4. All patients in the PEGASUS trial were receiving eculizumab at baseline, whereas patients in the APPLY-PNH trial were receiving either eculizumab or ravulizumab. The submission argued that differences between the trials in C5 inhibitor therapy were not expected to impact the indirect treatment comparison given that ravulizumab is a pharmacological analogue of eculizumab, and the PBAC had previously considered ravulizumab as non-inferior in effectiveness and safety compared to eculizumab. This claim was considered uncertain during evaluation as differences in treatments and treatment doses may impact the frequency of breakthrough haemolytic events.

Comparative effectiveness

APPLY-PNH trial

* 1. Table 4 presents the results for the primary outcomes in the APPLY-PNH trial.

Table 4: Results for the primary outcomes in the APPLY-PNH trial (24 weeks)

|  | Iptacopan  N=62 | C5 inhibitor  N=35 | Difference in marginal proportion (95% CI) | Ratio of marginal proportion  (95% CI) |
| --- | --- | --- | --- | --- |
| **Increase in haemoglobin levels ≥2 g/dL from baseline a** | | | | |
| n/N | 51/60 | 0/35 | **80.2 (71.2, 87.6)** | **40.2 (20.7, 74.8)** |
| Marginal proportion, % (95% CI) | 82.3 (73.4, 90.2) | 2.0 (1.1, 4.1) |
| **Achievement of a haemoglobin level ≥12 g/dL a** | | | | |
| n/N | 42/60 | 0/35 | **67.0 (56.4, 76.9)** | **38.2 (16.9, 78.6)** |
| Marginal proportion, % (95% CI) | 68.8 (58.3, 78.9) | 1.8 (0.9, 4.0) |

Source: Table 2-15, of the submission.

a To meet the response criteria for each of the primary outcomes, patients were required to have not received a transfusion or meet one of the pre-defined criteria for transfusion (haemoglobin between >7 g/dL and ≤9 g/dL with signs/symptoms of sufficient severity to warrant a transfusion or haemoglobin ≤7 g/dL regardless of presence of clinical signs and/or symptoms).

* 1. Treatment with iptacopan was associated with a statistically significant improvement compared to treatment with a C5 inhibitor for each of the primary outcomes.
  2. Based on extended follow-up to 48 weeks (in which patients in the iptacopan arm continued to receive iptacopan, and patients in the C5 inhibitor arm switched to iptacopan), 86.4% of patients (51/62) in the iptacopan arm and 72.4% of patients (21/34) in the C5 inhibitor arm who switched to iptacopan achieved an increase in haemoglobin level ≥2 g/dL without receiving or meeting the criteria for a blood transfusion.
  3. Based on extended follow-up at 48 weeks 67.8% of patients (40/62) in the iptacopan arm and 58.6% of patients (17/34) in the C5 inhibitor arm who switched to iptacopan achieved a haemoglobin level ≥12 g/dL without receiving or meeting the criteria for a blood transfusion.
  4. Table 5 presents the results for the change from baseline in haemoglobin level in the APPLY-PNH trial, based on the 24-week randomised treatment period.

Table 5: Results for the change from baseline in haemoglobin level in the APPLY-PNH trial (24 weeks)

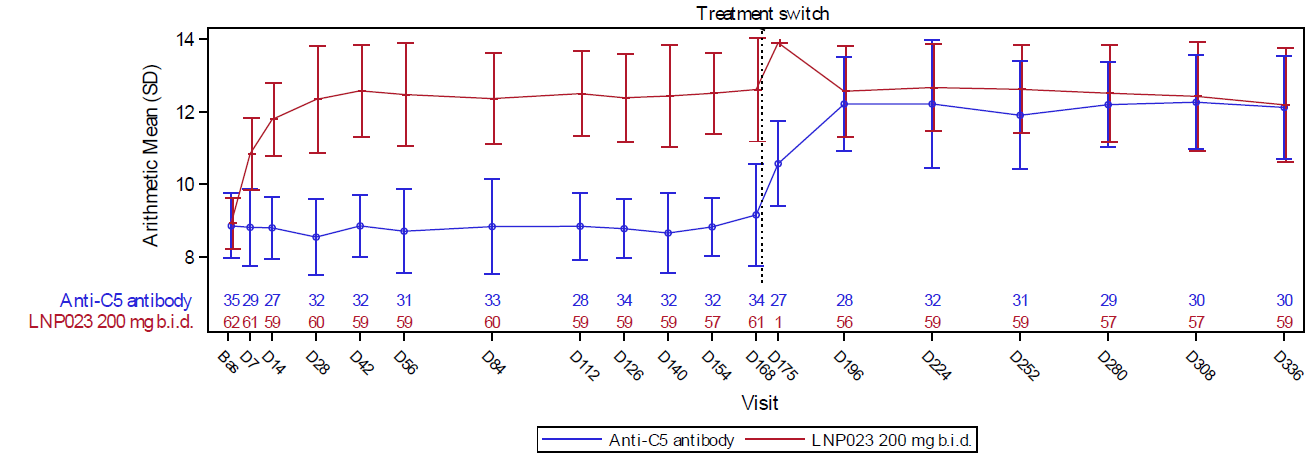
|  | Iptacopan  N=62 | C5 inhibitor  N=35 | Adjusted mean difference (95% CI) |
| --- | --- | --- | --- |
| Baseline haemoglobin, g/dL (SD) | 8.9 (0.704) | 8.85 (0.898) | **3.66 (****3.20, 4.12)** |
| Adjusted mean change from baseline (95% CI) | 3.60 (3.33, 3.88) | -0.06 (-0.45, 0.34) |

Source: Table 2-19, of the submission.

Abbreviations: CI, confidence interval; SD, standard deviation.

* 1. Treatment with iptacopan was associated with a statistically significant improvement in the change from baseline in haemoglobin level compared to treatment with a C5 inhibitor.
  2. Figure 1 presents the mean haemoglobin over time for the iptacopan and C5 inhibitor arms, based on extended follow-up to 48 weeks.

Figure 1: Arithmetic mean (SD) haemoglobin over time in the APPLY-PNH trial (48 weeks)



Source: Figure 2-9, of the submission.

Abbreviations: b.i.d., twice daily; D, Day; LP023, iptacopan; SD, standard deviation.

* 1. Based on extended follow-up to 48 weeks, improvements in haemoglobin level among patients in the iptacopan arm were generally maintained, and patients in the C5 inhibitor arm who switched to iptacopan also achieved a sustained increase in the mean haemoglobin level.
  2. Treatment with iptacopan was associated with a statistically significant improvement in the proportion of patients avoiding a blood transfusion compared to treatment with a C5 inhibitor (difference: 68.9%; 95% CI: 51.4%, 83.9%). Based on extended follow-up to 48 weeks, 82.3% of patients (51/62) in the iptacopan arm did not require a blood transfusion. For patients in the C5 inhibitor arm who switched to iptacopan, 91.2% of patients (31/34) did not require a transfusion from Day 1 of initiation of iptacopan.
  3. Treatment with iptacopan was associated with a lower rate of breakthrough haemolysis compared to treatment with a C5 inhibitor. The difference was statistically significant based on the reported rate ratio (rate ratio: 0.10; 95% CI: 0.02, 0.61) but not for the reported rate difference (rate difference: -0.60; 95% CI: ‑1.24, 0.04). Based on extended follow-up to 48 weeks, 6 patients (9.7%) in the iptacopan group and 7 patients (20.0%) randomised to the C5 inhibitor arm had at least one clinical breakthrough haemolysis event. Of the 7 patients in the C5 inhibitor arm, one patient (2.9%) experienced a clinical breakthrough haemolysis event after the start of iptacopan treatment. Overall, there were 8 clinical breakthrough haemolysis events in 7 patients during iptacopan treatment, with an adjusted annualised clinical breakthrough haemolysis rate of 0.11 (95% CI: 0.05, 0.23).
  4. During the 24-week randomised treatment period, one patient in the iptacopan arm experienced a major adverse vascular event (transient ischaemic attack) that was considered by the investigator to be unrelated to iptacopan. No patients in the C5 inhibitor arm experienced a major adverse vascular event. Based on extended follow-up to 48 weeks, one additional patient in the iptacopan arm experienced a major adverse vascular event (event not specified) and one patient in the C5 inhibitor arm experienced a major adverse vascular event after switching to iptacopan (hepatic/portal vein thrombosis).
  5. Table 6 presents the results for the change from baseline in FACIT-Fatigue score in the APPLY-PNH trial, based on the 24-week randomised treatment period.

Table 6: Results for the change from baseline in FACIT-Fatigue score in the APPLY-PNH trial (24 weeks)

|  | Iptacopan  N=62 | C5 inhibitor  N=35 | Adjusted mean difference (95% CI) |
| --- | --- | --- | --- |
| n/N | 62/62 | 31/35 | 8.29 (5.28, 11.29) |
| Baseline mean score (SD) | 34.7 (9.8) | 30.8 (11.5) |
| Adjusted mean change from baseline (95% CI) | 8.59 (6.72, 10.47) | 0.31 (-2.20, 2.81) |

Source: Table 2-29, of the submission.

Abbreviations: CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; SD, standard deviation.

FACIT-Fatigue scored from 0 to 52 with a higher score reflecting a lower symptom burden.

* 1. Treatment with iptacopan was associated with a statistically significant improvement in FACIT-Fatigue score compared to treatment with a C5 inhibitor (mean difference: 8.29; 95% CI: 5.28, 11.29). The submission argued that, based on the minimal clinically important difference of 5 points proposed by Cella et al. (2023), the result represented a clinically important improvement in FACIT-Fatigue score.
  2. Based on extended follow-up to 48 weeks, the adjusted mean change from baseline in FACIT-Fatigue score was 9.80 points (95% CI: 8.04, 11.56) in the iptacopan arm and 10.96 points (95% CI: 8.58, 13.34) among patients in the C5 inhibitor arm who switched to iptacopan. Improvements in the FACIT-Fatigue score in the iptacopan arm and among patients who switched to iptacopan from a C5 inhibitor appeared to be maintained over the follow-up period.
  3. Overall, the ESC noted the significant improvement in outcomes with iptacopan compared to treatment with a C5 inhibitor, for patients non-responsive to a C5 inhibitor.

Bucher method indirect comparison of iptacopan versus pegcetacoplan

* 1. The submission presented Bucher method indirect comparisons of iptacopan versus pegcetacoplan for the change from baseline in haemoglobin level (censored at transfusion), the proportion of patients remaining free from a blood transfusion, the change from baseline in absolute reticulocyte count, the proportion of patients experiencing breakthrough haemolysis, the change from baseline in FACIT-Fatigue score, and the proportion of patients experiencing selected adverse events.
  2. The results of the Bucher method indirect comparisons should be interpreted with caution due to differences between the APPLY-PNH and PEGASUS trials in common reference arms, trial eligibility criteria, timing of outcome assessments, outcome definitions/methods of analysis, and baseline patient characteristics. In particular, there were large differences between the common reference arms for most of the outcomes suggesting that the results of the Bucher method indirect comparisons may not be reliable.
  3. Table 7 presents the results of the Bucher method indirect comparison of iptacopan versus pegcetacoplan for the change from baseline in haemoglobin level (censored at transfusion).

Table 7: Results for the indirect comparison of change from baseline in haemoglobin level (censored at transfusion)

| Trial | Change from baseline in haemoglobin level (censored at transfusion) | | | Adjusted difference (95% CI) |
| --- | --- | --- | --- | --- |
| Iptacopan  Hb, g/dL | C5 inhibitor  Hb, g/dL | Pegcetacoplan  Hb, g/dL |
| APPLY-PNH | Baseline mean (SD):  8.90 (0.703) | Baseline mean (SD):  8.85 (0.898) | - | **3.66 (3.20, 4.12)** |
| Adjusted mean change (95% CI):  3.60 (3.33, 3.88) | Adjusted mean change (95% CI):  -0.06 (-0.45, 0.34) | - |
| PEGASUS | - | Baseline mean (SD): 8.68 (0.89) | Baseline mean (SD): 8.69 (1.08) | **3.84 (2.33, 5.34)** |
| - | Adjusted mean change (SE):  -1.47 (0.67) | Adjusted mean change (SE): 2.37 (0.36) |
| **Indirect comparison of iptacopan vs. pegcetacoplan** | | | | -0.18 (-1.75, 1.39) |

Source: Table 2-45, of the submission.

Abbreviations: CI, confidence interval; Hb, haemoglobin; SD, standard deviation; SE, standard error.

Bolded results reflect nominal statistical significance.

* 1. Based on the indirect comparison, treatment with iptacopan was associated with a smaller improvement in haemoglobin from baseline compared to pegcetacoplan, but the difference was not statistically significant.
  2. There were similarly no statistically significant differences between iptacopan and pegcetacoplan in the proportion of patients remaining free from transfusion (risk difference = 5.9%; 95% CI: -15.9, 27.7); the proportion of patients experiencing breakthrough haemolysis (risk difference: -0.01; 95% CI: -0.20, 0.18); and change from baseline in FACIT-Fatigue score (mean difference: -3.61; 95% CI: -10.66, 3.44).

Matching-adjusted indirect comparisons

* 1. The submission presented anchored and unanchored MAICs of iptacopan versus pegcetacoplan using individual patient data for iptacopan from the APPLY-PNH trial and summary-level data for pegcetacoplan from the PEGASUS trial. Comparisons were presented for the change from baseline in haemoglobin (censored at transfusion), the change from baseline in haemoglobin (not censored at transfusion), the proportion of patients remaining free from a blood transfusion, the change from baseline in lactate dehydrogenase level, the change from baseline in FACIT-Fatigue score, and the proportion of patients who experienced a serious adverse event.
  2. The submission argued that the results of the anchored MAICs may be biased against iptacopan, due to the observed worsening of outcomes among patients in the eculizumab arm of the PEGASUS trial after cessation of pegcetacoplan. The submission noted that unanchored MAICs comparing the C5 inhibitor arm of the APPLY-PNH trial and the eculizumab arm of the PEGASUS trial included in the MAIC technical report also suggested moderate to large differences in response for all outcomes apart from the change from baseline in haemoglobin (not censored for transfusion). Given the differences in the control arms between studies, the submission considered that the unanchored MAICs of iptacopan versus pegcetacoplan represented the most suitable analyses for the base case.
  3. The submission stated that the APPLY-PNH trial population was initially aligned based on eligibility criteria to the PEGASUS trial. Of the 62 patients randomised to the iptacopan arm of APPLY-PNH, 54 remained after alignment of the eligibility criteria for the PEGASUS trial. The submission noted that differences between the APPLY-PNH and PEGASUS trials in eligibility criteria for haemoglobin (<10.0 g/dL for the APPLY-PNH trial versus <10.5 g/dL for the PEGASUS trial) could not be aligned as the APPLY-PNH trial inclusion criterion was narrower than the PEGASUS trial inclusion criterion.
  4. The submission stated that 6 variables were identified and ranked in order of priority for adjustment in the MAIC analyses: baseline haemoglobin, female sex, transfusion-free 12 months prior to baseline, baseline reticulocytes, baseline lactate dehydrogenase, and age. Anchored MAICs should adjust for all relevant treatment effect modifiers, whereas unanchored MAICs should adjust for all relevant treatment effect modifiers as well as prognostic variables. The status of the 6 ranked variables as either prognostic or treatment effect modifier variables (or both) was not addressed in the submission. Additionally, it is unclear whether all relevant treatment effect modifier and prognostic variables were identified, as details of the process used to identify the treatment effect modifier and prognostic variables for each of the outcomes were not provided.
  5. Six different scenarios (A to F), based on the 6 ranked variables were considered for the MAICs. The MAIC base case was based on Scenario D in which 3 variables were matched (haemoglobin at baseline, female sex and the proportion of patients who are transfusion-free in the prior 12 months). The submission stated that these 3 variables were chosen in order to achieve a balance between the number of included variables and the resulting effective sample size. Limiting the number of variables to 3 in order to preserve the effective sample size did not appear to be reasonable. The low effective sample size after matching suggests that the trial sample size was insufficient and/or there was a lack of overlap between the trial populations. The Pre-Sub-Committee Response (PSCR) stated that the submission presented all available data for this rare patient population.
  6. The MAIC analyses weighted continuous variables in the APPLY-PNH to match the published means and standard deviations reported in the PEGASUS trial. In the base case analyses (based on 3 included variables), the only included continuous variable was the baseline haemoglobin.
  7. Matching based on the 3 selected variables (baseline haemoglobin, female sex, proportion who were transfusion-free in the prior 12 months) resulted in an effective sample size of 16. The results of the unanchored MAIC are unlikely to be reliable given the very low effective sample size after matching. Additionally, based on examination of the histogram of patient weights for the base case analysis, one patient contributed an equivalent weight of approximately 7 patients to the effective sample size. Based on the post-matching characteristics, there were residual differences in a number of variables, including the platelet count at screening, the time since diagnosis, the FACIT-Fatigue score, the proportion with a history of aplastic anaemia, the proportion with ≥4 transfusions in the prior 12 months, and the proportion with White race. Some of these variables may represent treatment effect modifier or prognostic variables. The ESC acknowledged that one patient having such a high weight was a large source of uncertainty. However, the ESC considered that no clear guidance was evident in the literature on what distribution of weights is acceptable, or on the treatment of outlying weights. Acknowledging the methodological limitations outlined above, the ESC considered that the unanchored MAICs of iptacopan versus pegcetacoplan had merit and were informative given the differences in the common reference arms between studies.
  8. The submission noted that due to the 4-week run in period in the PEGASUS trial, the Week 16 efficacy endpoint for pegcetacoplan-treated patients included 20 weeks of pegcetacoplan treatment. To approximate this for the APPLY-PNH trial, outcomes were reassessed in a *post hoc* analysis based on a similar duration of treatment in the APPLY-PNH trial (i.e., APPLY-PNH data was assessed up to Week 20). Additionally, the individual patient data from the APPLY-PNH trial were used to recalculate outcomes using similar methods of analysis to the methods used in the PEGASUS trial.
  9. Table 8 presents the results of the unanchored MAIC of change from baseline in haemoglobin (censored at transfusion).

Table 8: Unanchored MAIC of results for the change from baseline in haemoglobin (censored at transfusion)

| Comparison | Pegcetacoplan  (PEGASUS)  Mean change from baseline (95% CI) | Iptacopan  (APPLY-PNH)  Mean change from baseline (95% CI) | Mean difference (95% CI) |
| --- | --- | --- | --- |
| Naïve comparison a | N=41  2.37 (1.66, 3.08) | N=62  3.63 (3.34, 3.93) | NR |
| Unmatched and unadjusted b | N=41  2.37 (1.66, 3.08) | N=62  3.31 (3.00, 3.62) | **0.94 (0.17, 1.71)** |
| Matched and unadjusted c | N=41  2.37 (1.66, 3.08) | N=54  3.35 (3.00, 3.69) | **0.98 (0.19, 1.76)** |
| Matched and adjusted d | N=41  2.37 (1.66, 3.08) | ESS=16  3.68 (3.33, 4.04) | **1.31 (0.52, 2.10)** |

Source: Table 2-53,; Appendix Table 19, of the MAIC technical report, Attachment 9 of the submission.

Abbreviations: CI, confidence interval; ESS, effective sample size; NR, not reported.

a Iptacopan results based on reported outcomes at 24 weeks with no adjustment for differences in outcome definitions between trials.

b Iptacopan results recalculated using the PEGASUS trial outcome definition/method of analysis; iptacopan results based on *post hoc* analysis of outcomes at 20 weeks to approximate the follow-up duration in the PEGASUS trial.

c Iptacopan results based on exclusion of patients who did not meet the eligibility criteria for the PEGASUS trial.

d Includes adjustment for imbalances in 3 variables (baseline haemoglobin per PEGASUS definition, sex, and proportion of patients who were transfusion-free within 12 months prior to baseline), with continuous variables (haemoglobin) matched based on mean and standard deviation.

* 1. Based on the matched and adjusted results for the unanchored MAIC, treatment with iptacopan was associated with a nominally statistically significant improvement in change from baseline in haemoglobin (censored at transfusion) compared to pegcetacoplan (mean difference: 1.31; 95% CI: 0.52, 2.10). Based on the anchored MAIC, the mean difference favoured iptacopan, but was not statistically significant (mean difference: 0.05; 95% CI: -1.56, 1.67).
  2. Table 9 presents the results of the unanchored MAIC of the proportion of patients who avoided a blood transfusion.

Table 9: Unanchored MAIC of results for the proportion of patients remaining free from a blood transfusion

| Comparison | Pegcetacoplan  (PEGASUS)  Transfusion free, n (%) | Iptacopan  (APPLY-PNH)  Transfusion free, n (%) | Odds ratio (95% CI) |
| --- | --- | --- | --- |
| Naïve comparison a | N=41  35 (85.4%) | N=62  59 (95.2%) | NR |
| Unmatched and unadjusted b | N=41  35 (85.4%) | N=62  60 (96.8%) | 5.14 (0.98, 26.88) |
| Matched and unadjusted c | N=41  35 (85.4%) | N=54  52 (96.3%) | 4.46 (0.85, 23.36) |
| Matched and adjusted d | N=41  35 (85.4%) | ESS=16  NR (98.2%) | **9.17 (1.59, 52.89)** |

Source: Table 2-54,; Appendix Table 20, of the MAIC technical report, Attachment 9 of the submission.

Abbreviations: CI, confidence interval; ESS, effective sample size; NR, not reported.

a Iptacopan results based on reported outcomes at 24 weeks with no adjustment for differences in outcome definitions between trials.

b Iptacopan results recalculated using the PEGASUS trial outcome definition/method of analysis; iptacopan results based on *post hoc* analysis of outcomes at 20 weeks to approximate the follow-up duration in the PEGASUS trial.

c Iptacopan results based on exclusion of patients who did not meet the eligibility criteria for the PEGASUS trial.

d Includes adjustment for imbalances in 3 variables (baseline haemoglobin per PEGASUS definition, sex, and proportion of patients who were transfusion-free within 12 months prior to baseline), with continuous variables (haemoglobin) matched based on mean and standard deviation.

* 1. Based on the matched and adjusted results for the unanchored MAIC, treatment with iptacopan was associated with an improvement in the proportion of patients who avoided a blood transfusion compared to pegcetacoplan, and the difference was statistically significant (odds ratio: 9.17; 95% CI: 1.59, 52.89). Based on the anchored MAIC, the odds ratio favoured iptacopan, but the difference was not statistically significant (odds ratio: 2.70; 95% CI: 0.31, 23.77).
  2. Based on the matched and adjusted results for the unanchored MAIC, treatment with iptacopan was associated with an increase in LDH level, whereas pegcetacoplan was associated with a decrease in LDH level. The mean difference between treatments favoured pegcetacoplan but was not statistically significant (mean difference: 36.68; 95% CI: -62.54, 135.89). Based on the anchored MAIC, the mean difference favoured iptacopan, but was not statistically significant (mean difference: -8.45; 95% CI: -194.92, 178.02).
  3. Based on the matched and adjusted results for the unanchored MAIC, treatment with iptacopan was associated with a smaller improvement in FACIT-Fatigue score compared to pegcetacoplan, but the difference was not statistically significant (mean difference: -2.32; 95% CI: -6.34, 1.70). Based on the anchored MAIC, the mean difference favoured pegcetacoplan, but the difference was not statistically significant (mean difference: -2.96; 95% CI: -10.65, 4.73).

Comparative harms

APPLY-PNH trial

* 1. Table 10 presents a summary of adverse event results for the APPLY-PNH trial, based on the 24-week randomised treatment period.

Table 10: Summary of adverse events in the APPLY-PNH trial (24 weeks)

|  | Iptacopan  N=62 | C5 inhibitor  N=35 |
| --- | --- | --- |
| Any AE, n (%)  - Treatment-related AE | 51 (82.3)  16 (25.8) | 28 (80.0)  3 (8.6) |
| Severe AE, n (%)  - Treatment-related AE | 3 (4.8)  0 (0.0) | 3 (8.6)  0 (0.0) |
| Serious AE, n (%)  - Treatment-related AE | 6 (9.7)  1 (1.6) | 5 (14.3)  0 (0.0) |
| Fatal serious AE, n (%) | 0 (0.0) | 0 (0.0) |
| AE leading to treatment discontinuation, n (%) | 0 (0.0) | 0 (0.0) |
| AE requiring additional therapy, n (%) | 40 (64.5) | 18 (51.4) |
| Any AE occurring in ≥5%, n (%) |  |  |
| - Headache | 10 (16.1) | 1 (2.9) |
| - Diarrhoea | 9 (14.5) | 2 (5.7) |
| - Nasopharyngitis | 7 (11.3) | 2 (5.7) |
| - Nausea | 6 (9.7) | 1 (2.9) |
| - Arthralgia | 5 (8.1) | 1 (2.9) |
| - COVID-19 | 5 (8.1) | 9 (25.7) |
| - Urinary tract infection | 5 (8.1) | 1 (2.9) |
| - Abdominal pain | 4 (6.5) | 1 (2.9) |
| - Blood LDH increased | 4 (6.5) | 3 (8.6) |
| - Dizziness | 4 (6.5) | 0 (0.0) |
| - Back pain | 3 (4.8) | 2 (5.7) |
| - Breakthrough haemolysis | 2 (3.2) | 6 (17.1) |
| - Pyrexia | 2 (3.2) | 3 (8.6) |
| - Sinusitis | 2 (3.2) | 3 (8.6) |
| - Upper respiratory tract infection | 2 (3.2) | 3 (8.6) |
| - Extravascular haemolysis | 0 (0.0) | 2 (5.7) |

Source: Table 2-34,; Table 2-35 of the submission; Table 12-3, pp145-146 of the APPLY-PNH clinical study report.

* 1. The proportion of patients experiencing at least one treatment-emergent adverse event during the 24-week randomised treatment period was similar between treatment arms (82.3% in the iptacopan arm versus 80.0% in the C5 inhibitor arm). The most commonly occurring events (>10% in either treatment arm) were headache (16.1% versus 2.9% in the iptacopan and C5 inhibitor arms, respectively), diarrhoea (14.5% versus 5.7%), nasopharyngitis (11.3% versus 5.7%), COVID-19 (8.1% versus 25.7%) and breakthrough haemolysis (3.2% versus 17.1%).
  2. A higher proportion of patients in the iptacopan arm experienced a treatment-related treatment-emergent adverse event. The most commonly reported events (>3% in either treatment arm) were headache (6.5% and 2.9% in the iptacopan and C5 inhibitor arms, respectively), arthralgia (4.8% versus 0%), nausea (4.8% versus 2.9%), diarrhoea (3.2% versus 0%), hot flush (3.2% versus 0%) and thrombocytopenia (3.2% versus 0%).
  3. Serious adverse events occurred in 9.7% of patients in the iptacopan arm and 14.3% of patients in the C5 inhibitor arm. The only serious adverse event that occurred in >1 patient in either treatment arm was COVID-19, occurring in 1 patient (1.6%) in the iptacopan arm and 2 patients (5.7%) in the C5 inhibitor arm. There were no fatal serious adverse events in either treatment arm.
  4. Based on the reported adverse events of special interest, treatment with iptacopan was associated with a numerically lower incidence of serious or severe infections (3.2% versus 8.6%) and PNH haemolysis and thrombosis events (16.1% versus 28.6%), and a numerically higher incidence of decreased platelets (6.5% versus 0%) compared to the C5 inhibitor arm.
  5. Based on extended follow-up to 48 weeks, serious adverse events occurred in 14.5% of patients (9/62) patients randomised to iptacopan and in an additional four patients in the C5 inhibitor arm who switched to iptacopan. Overall, 13.5% of patients (13/96) who received iptacopan experienced a serious adverse event. No serious adverse event occurred in more than one patient.
  6. The submission provided the European Union safety risk management plan along with the Australian Specific Annex. Important identified risks for iptacopan include infections caused by encapsulated bacteria. Important potential risks include serious haemolysis following discontinuation of iptacopan. Missing information includes use in pregnant patients and long-term safety.

Bucher method indirect comparison of iptacopan versus pegcetacoplan

* 1. The submission presented Bucher method indirect comparisons of selected summary events, the proportion of patients with a serious adverse event of breakthrough haemolysis, and selected treatment-emergent adverse events occurring in >5% of patients in the APPLY-PNH or PEGASUS trials.
  2. Table 11 presents the results of the Bucher method indirect comparison of iptacopan versus pegcetacoplan for selected summary adverse events (treatment-emergent adverse events, serious adverse events, treatment-emergent adverse events leading to discontinuation).

Table 11: Results of the indirect comparison for selected summary adverse events

| Adverse event | Iptacopan vs  C5 inhibitor | Pegcetacoplan vs eculizumab | Indirect estimate (95% CI) |
| --- | --- | --- | --- |
| **Treatment-emergent AE** | | | |
| Risk ratio (95% CI) | 1.03 (0.84, 1.26) | 1.01 (0.85, 1.19) | 1.02 (0.78, 1.33) |
| Risk difference (95% CI) | 0.02 (-0.14, 0.18) | 0.01 (-0.14, 0.15) | 0.01 (-0.21, 0.23) |
| **Serious AE** | | | |
| Risk ratio (95% CI) | 0.68 (0.22, 2.06) | 1.11 (0.41, 3.01) | 0.61 (0.14, 2.74) |
| Risk difference (95% CI) | -0.05 (-0.18, 0.09) | 0.02 (-0.14, 0.18) | -0.07 (-0.28, 0.14) |
| **Treatment-emergent AE leading to discontinuation** | | | |
| Risk ratio (95% CI) | NE | NE | NE |
| Risk difference (95% CI) | 0 (0, 0) | 0.07 (-0.01, 0.16) | -0.07 (-0.16, 0.02) |

Source: Table 2-48, of the submission.

Abbreviations: AE, adverse event; CI, confidence interval; NE, not estimable.

* 1. Based on the indirect comparison, there were no statistically significant differences in summary treatment-emergent adverse events, serious adverse events or treatment-emergent adverse events leading to discontinuation. The safety comparisons were based on a relatively short duration of follow-up.
  2. The submission noted that the only commonly reported serious adverse event in the APPLY-PNH and PEGASUS trials was breakthrough haemolysis. Table 12 presents a comparison of the occurrence of serious adverse events of breakthrough haemolysis for the APPLY-PNH and PEGASUS trials.

Table 12: Results of the indirect comparison for serious adverse events of breakthrough haemolysis

| Adverse event | Iptacopan vs  C5 inhibitor | Pegcetacoplan vs eculizumab | Indirect estimate (95% CI) |
| --- | --- | --- | --- |
| Relative risk (95% CI) | NE | 1.9 (0.18, 20.15) | NE |
| Risk difference (95% CI) | -0.03 (-0.07, 0.01) | 0.02 (-0.06, 0.11) | -0.05 (-0.144, 0.044) |

Source: Table 2-51, of the submission.

Abbreviations: CI, confidence interval; NE, not estimable.

* 1. Based on the indirect comparison of serious adverse events of breakthrough haemolysis, there was no statistically significant difference between iptacopan and pegcetacoplan.
  2. Based on the indirect comparison of treatment-emergent adverse events occurring in >5% of patients, treatment with iptacopan was associated with a nominally statistically significant increase in the proportion of patients experiencing headache (risk difference: 0.29; 95% CI: 0.088, 0.492). There was no statistically significant difference for any of the other adverse events. The submission noted that injection site reactions were the most frequently reported adverse event associated with pegcetacoplan treatment, but that these were not applicable (hence not reported) in the APPLY-PNH trial given that iptacopan is an oral treatment.

Matching-adjusted indirect comparisons

* 1. The submission presented MAICs comparing the proportion of patients who experienced a serious adverse event. Based on the matched and adjusted results for the unanchored MAIC, treatment with iptacopan was associated with a lower rate of serious adverse events compared to pegcetacoplan, and the difference was nominally statistically significant (odds ratio: 0.24; 95% CI: 0.06, 0.98). Based on the anchored MAIC, the odds ratio favoured iptacopan, but the difference was not statistically significant (odds ratio: 0.13; 95% CI: 0.01, 1.23). The relevance of the 3 matched variables (baseline haemoglobin, female sex, the proportion who received a blood transfusion in the prior 12 months) to the proportion of patients experiencing a serious adverse event was unclear.

Benefits/harms

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

Clinical claim

* 1. The submission described iptacopan as non-inferior in terms of effectiveness and safety compared to pegcetacoplan, in patients with persistent anaemia despite C5 inhibitor therapy.
  2. The evaluation considered the therapeutic conclusion presented in the submission was not adequately supported.

The results of the Bucher method indirect comparisons were considered highly uncertain due to major differences between the APPLY-PNH and PEGASUS trials (including differences in common reference arm treatments, eligibility criteria, timing of outcome assessments, outcome definitions/methods of analysis, and baseline patient characteristics), which impacted the assessment of the comparative effectiveness and safety of iptacopan and pegcetacoplan.

The submission attempted to address some of the differences in eligibility criteria, timing of outcome assessments, outcome definitions/methods of analysis, and patient characteristics using MAICs. However, the effective sample size after partial alignment of trial eligibility criteria and matching for 3 patient characteristics in the MAICs was very low, suggesting that the comparisons are unlikely to be reliable. Additionally, the effective sample size was dominated by a single patient with a large weighting (equivalent to approximately 7 patients), the status of the 3 included variables as either treatment effect modifiers or prognostic variables (or both) was not adequately addressed in the submission, MAICs did not appear to include all relevant treatment effect modifier and prognostic variables, and no non-inferiority margins for the indirect comparisons were nominated in the submission.

* 1. The ESC acknowledged that the comparative clinical evidence had limitations but considered the APPLY-PNH trial showed iptacopan was an effective therapy in patients unresponsive to C5 inhibitors. The majority of the clinical outcomes used in the indirect comparative analyses were objective and relevant in this treatment space, with results across all the anchored analyses showing wide and overlapping confidence intervals. The ESC acknowledged the transitivity concerns between the APPLY-PNH and PEGASUS trials and the remaining methodological limitations of the indirect comparisons; however, in the context of this rare disease, the ESC considered it was reasonable to accept the claim of non-inferior effectiveness given the results of the unanchored MAIC either found no significant difference between iptacopan and pegcetacoplan or reported a nominal statistically significant difference in favour of iptacopan.
  2. The evaluation noted the comparative clinical evidence from APPLY-PNH was limited to 24 weeks, and as such the longer-term effectiveness of iptacopan treatment on the incidence of breakthrough haemolysis and thrombotic events is unclear. The PSCR noted that patients in the APPLY-PNH trial entered an open label extension period to 48 weeks and stated that no serious haemolysis treatment emergent adverse events occurred with iptacopan over that period. The ESC noted that 48 weeks of evidence was provided in the final analysis. The ESC considered that, whilst the additional 24 weeks of data was not comparative and this is still relatively short for a lifetime treatment, there was no increased incidence of breakthrough haemolysis or thrombotic events.
  3. The ESC noted the comparative harms presented showed similar rates of AEs between iptacopan and pegcetacoplan. Overall, the ESC agreed with the submission claim of non-inferior safety, noting the safety comparisons were based on a relatively short duration of follow-up.
  4. The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable in the context of this rare disease.
  5. The PBAC considered that the claim of non-inferior comparative safety was reasonable in the context of this rare disease.

Economic analysis

* 1. The submission presented a cost-minimisation of iptacopan versus pegcetacoplan for the treatment of adults with PNH who have inadequate clinical response to C5 inhibitor treatment. Key components of the cost-minimisation approach are summarised in Table 13.

Table 13: Key components and assumptions of the cost-minimisation approach

|  |  |
| --- | --- |
| Component | Claim or assumption |
| Therapeutic claim: effectiveness | Based on evidence presented, effectiveness was claimed to be non-inferior. |
| Therapeutic claim: safety | Based on evidence presented, safety was claimed to be non-inferior. |
| Evidence base | Bucher method indirect comparison of iptacopan (APPLY-PNH) versus pegcetacoplan (PEGASUS) using the trial control arms (APPLY-PNH: eculizumab or ravulizumab; PEGASUS: eculizumab) as common reference.  Anchored MAIC of iptacopan (APPLY-PNH) versus pegcetacoplan (PEGASUS) using the trial control arms (APPLY-PNH: eculizumab or ravulizumab; PEGASUS: eculizumab) as common reference.  Unanchored MAIC of iptacopan (APPLY-PNH) versus pegcetacoplan (PEGASUS). |
| Equi-effective doses | Iptacopan 145,600 mg (200 mg twice a day x 13 packs per year) is equivalent to pegcetacoplan 116,365 mg (1,080 mg x 107.7 injections per year). |
| Direct medicine costs | The annual cost of treatment with iptacopan was assumed to be lower than pegcetacoplan, due to the inclusion of additional costs associated with coadministration of a C5 inhibitor (ravulizumab) during the initial 4 weeks of pegcetacoplan treatment. |
| Other costs or cost offsets | Included drug and administration costs for concomitant C5 inhibitor therapy (ravulizumab) during the initial 4 weeks of treatment with pegcetacoplan. |

Source: Table 3-1, of the submission.

* 1. The submission argued that, based on the claim of non-inferiority for iptacopan versus pegcetacoplan, the derivation of equi-effective doses based on the doses used in the clinical trials (APPLY-PNH and PEGASUS, respectively) was appropriate.
  2. The equi-effective dose for iptacopan was based on the dosing used in the APPLY-PNH trial (200 mg twice daily). The submission estimated a total dose of 145,600 mg per year (200 mg x 56 capsules/pack x 13 packs/year). The assumed dose of 200 mg twice daily is consistent with the dose used in the APPLY-PNH trial and the draft product information. Dose increases were not permitted in the APPLY-PNH trial, and the draft product information does not include any recommendations relating to dose increases for iptacopan. The proposed total dose included in the proposed equi-effective dose relationship equated to 364 days of treatment with iptacopan, due to rounding of the number of packs per year to 13 packs (145,600 mg ÷ 400 mg = 364 days). This differed from the calculation included in the cost-minimisation, which assumed 365 days per year, equating to 13.04 packs (400 mg x 13.04 packs = 146,048 mg). The proposed equi-effective dose for iptacopan assumes perfect adherence to treatment.
  3. The equi-effective dose for pegcetacoplan was based on the dose included in the July 2022 pegcetacoplan submission, in which pegcetacoplan was cost-minimised to ravulizumab over a 52-week maintenance treatment period (paragraph 5.5, pegcetacoplan, Public Summary Document (PSD), July 2022 PBAC meeting). The equi-effective pegcetacoplan dose of 116,365 mg (1,080 mg x 107.7 injections) reflected the doses of pegcetacoplan used in the PEGASUS trial. In the PEGASUS trial, patients initiated pegcetacoplan at a dose of 1,080 mg twice a week but may have increased to 1,080 mg every third day if they did not respond sufficiently to treatment. Details of the method and assumptions used to derive the number of pegcetacoplan injections (including any adjustments for treatment adherence) were not included in the July 2022 pegcetacoplan PSD. However, the number of injections included in the cost-minimisation (equating to 2.07 doses per week) suggests that a proportion of patients were assumed to require a dose frequency greater than twice a week.
  4. The proposed equi-effective doses for iptacopan and pegcetacoplan were:

Iptacopan 145,600 mg (200 mg/capsule × 56 capsules/pack × 13 packs) is equivalent to pegcetacoplan 116,365 mg (1,080 mg/vial × 107.7 injections).

If corrected for 365 days instead of 364 days, the equi-effective doses for iptacopan and pegcetacoplan were:

Iptacopan 146,048 mg (200 mg/capsule × 56 capsules/pack × 13.04 packs) is equivalent to pegcetacoplan 116,365 mg (1,080 mg/vial × 107.7 injections).

* 1. The submission noted that the product information for pegcetacoplan states that patients switching from a C5 inhibitor to pegcetacoplan are required to continue treatment with the C5 inhibitor during the initial 4 weeks of pegcetacoplan treatment; and that this differs from iptacopan, which does not require concurrent treatment with a C5 inhibitor during the initial 4 weeks. Costs associated with the use of a C5 inhibitor during the initial 4 weeks of pegcetacoplan treatment were included in the cost-minimisation to iptacopan. The inclusion of this cost did not appear to be appropriate given that the PBAC Guidelines v5.0 note that for medicines that are ongoing, a steady state dose comparison is generally most relevant. Iptacopan and pegcetacoplan are both chronic therapies that are expected to be used lifelong.
  2. The submission noted that the pegcetacoplan sponsor proposed a percentage rebate of the cost of the initial month of pegcetacoplan treatment (i.e., when used in combination with a C5 inhibitor), but that the percentage rebate is unknown due to being redacted in the July 2022 pegcetacoplan PSD (paragraph 1.10, pegcetacoplan, PSD, July 2022 PBAC meeting). In the absence of information relating to the rebate, the full cost of C5 inhibitor treatment over the initial 4-week pegcetacoplan treatment period was included in the cost-minimisation. The PSCR stated that the pegcetacoplan rebates are assumed to be considered within the special pricing arrangements and hence the cost-minimisation approach presented will also include these rebates when the arrangements can be shared.
  3. The submission’s cost-minimisation approach included ravulizumab as a proxy for the cost associated with C5 inhibitor therapy during the initial 4 weeks treatment with pegcetacoplan. This was reasonable.
  4. The submission noted that pegcetacoplan is administered as a subcutaneous infusion using a commercially available infusion pump, and that, due to the complexity associated with administration of pegcetacoplan, a proportion of patients may not be able to self-administer treatment. However, in the absence of data on the proportion of patients who do not self-administer pegcetacoplan, administration costs for pegcetacoplan were excluded from the cost-minimisation. This was reasonable*.*
  5. The submission noted that, based on the respective product information documents for iptacopan and pegcetacoplan, the same vaccinations are required prior to initiating iptacopan and pegcetacoplan (*Neisseria meningitidis* types A, C, W, Y, and B; *Streptococcus pneumoniae* and *Haemophilus influenzae* type B), and therefore, costs associated with vaccination were not included in the cost-minimisation approach. This appeared reasonable.
  6. The cost-minimisation was conducted at the AEMP level, based on the published prices for pegcetacoplan and ravulizumab, over a 1-year time horizon (assumed to be the initial year of treatment with iptacopan). Pegcetacoplan and ravulizumab are both subject to special pricing arrangements.
  7. Table 14 presents the results of the cost-minimisation of pegcetacoplan versus iptacopan.

Table 14: Results of the cost-minimisation approach based on published prices

|  |  |  |
| --- | --- | --- |
| Component | Pegcetacoplan | Iptacopan |
| **Pegcetacoplan treatment cost** | | |
| Pegcetacoplan administrations in first year a | 107.7 | - |
| Pegcetacoplan cost (AEMP) in first year ($4,343.86 x 107.7) | $467,833.72 | - |
| Ravulizumab cost (AEMP) over initial 4 weeks ($21.91 per mg x 1,644 mg) b | $36,031.24 | - |
| Ravulizumab administration cost over initial 4 weeks (1 x $59.45) c | $59.45 | - |
| Total cost of pegcetacoplan treatment in first year | $503,924.41 | - |
| **Cost-minimisation of iptacopan** | | |
| Iptacopan cost over the first year | - | $503,924.41 |
| Iptacopan packs in first year d | - | 13.04 |
| Iptacopan cost (AEMP) in first year ($503,924.41 ÷ 13.04) | - | $38,657.22 |

Source: Derived using the ‘Cost-min analysis’ worksheet of the cost-minimisation Excel workbook, Attachment 10 of the submission.

Abbreviations: AEMP, approved ex-manufacturer price.

a Based on the number of pegcetacoplan injections included in the equi-effective dose relationship for pegcetacoplan versus ravulizumab in the July 2022 pegcetacoplan submission (paragraph 5.5, pegcetacoplan, Public Summary Document, July 2022 PBAC meeting).

b Based on the maintenance dosing of ravulizumab reported in the July 2022 pegcetacoplan Public Summary Document in the cost-minimisation of pegcetacoplan versus ravulizumab (21,375 mg), the submission assumed that 1,644 mg of ravulizumab would be required over 4 weeks (21,375 mg ÷ 52 weeks x 4 weeks).

c Based on the recommended dosing of ravulizumab every 8 weeks, the administration cost for 4 weeks of treatment was assumed to be 50% of the cost of MBS Item 13950 (parenteral administration of one or more antineoplastic agents).

d Iptacopan packs in first year based on 365 days per year and 28 days per pack.

* 1. Based on the cost-minimisation of iptacopan versus pegcetacoplan, the submission estimated an AEMP of $38,657.22 per pack of 56 x 200 mg iptacopan capsules, equating to a Section 100 public hospital DPMQ of $38,657.22 and a Section 100 private hospital DPMQ of $38,705.59. The submission acknowledged that the effective price and cost per patient will be lower than the numbers presented in the cost-minimisation, which are based on published prices.
  2. Based on exclusion of the drug and administration costs associated with ravulizumab (steady state dose comparison), the cost-minimised AEMP of iptacopan was $35,888.61.
  3. The ESC considered it was appropriate for iptacopan to be cost neutral to the PBS.

Drug cost/patient/year

* 1. Table 15 presents a comparison of drug costs for iptacopan and pegcetacoplan included in the cost-minimisation and financial estimates.

Table 15: Drug cost per patient for iptacopan and pegcetacoplan

|  | Clinical trial | Cost-minimisation | Financial estimates |
| --- | --- | --- | --- |
| **Iptacopan** | | | |
| Dose regimen | 200 mg twice daily | 200 mg twice daily | 200 mg twice daily |
| Cost per pack (56 x 200 mg capsules) | - | $38,657.22 | $38,657.22 |
| Scripts per year | - | 13.04 a | 13.00 b |
| Cost per patient per year | - | $503,924.41 | $502,543.86 |
| **Pegcetacoplan** | | | |
| Pegcetacoplan | | | |
| Dose regimen | 1,080 mg twice weekly or every third day c | 107.7 infusions of 1,080 mg per year | 107.7 infusions of 1,080 mg per year |
| Cost per 1,080 mg vial | - | $4,343.86 | $4,343.86 |
| Cost per patient per year | - | $467,833.72 | $467,573.09 d |
| Ravulizumab | | | |
| Dose regimen | NA e | One dose of 1,644 mg during initial 4 weeks of pegcetacoplan treatment f | One dose of 1,644 mg during initial 4 weeks of pegcetacoplan treatment f |
| Cost per mg | - | $21.91 | $21.91 |
| Cost per patient per year | - | $36,031.24 | Initial year: $36,031.24  Subsequent year: Nil |
| Total cost per patient per year of pegcetacoplan | - | $503,864.96 g | Initial year: $503,604.33  Subsequent year: $467,573.09 |

Source: Constructed during the evaluation using the Section 3 cost-minimisation Excel workbook (Attachment 10 of the submission) and the Section 4 utilisation and financial implications Excel workbook (Attachment 11 of the submission).

Abbreviations: NA, not applicable.

a Based on an assumption of 365 days per year.

b Based on an assumption of 52 weeks (=364 days) per year.

c Patients were permitted to increase to 1,080 mg every third day if they did not respond sufficiently to treatment.

d The cost per year was lower than the cost per year included in the cost-minimisation due to rounding of the number of vials per 4-week period to 2 decimal places in an earlier calculation step (107.7 ÷ 52 x 4 = 8.28 vials per script).

e Patients in the PEGASUS trial received eculizumab treatment during the initial 4 weeks.

f Based on assumed average ravulizumab dose of 3,244 mg every 8 weeks, the dose over a 4-week treatment period was assumed to be 1,622 mg (50% x 3,244 mg).

g The difference compared to iptacopan was due to the inclusion of ravulizumab administration costs in the cost-minimisation.

Estimated PBS usage & financial implications

* 1. This submission was considered by DUSC.
  2. The submission used a mixed epidemiological/market share approach to estimate the utilisation and financial implications of listing iptacopan for the treatment of adults with PNH who have inadequate clinical response to C5 inhibitor treatment.
  3. Table 16 presents the key data sources and parameter values applied in the utilisation and financial estimates.

Table 16: Key data sources and parameter values applied in the utilisation and financial estimates

| Data | Value applied and source | Comment |
| --- | --- | --- |
| Treatment utilisation | | |
| Prevalence of PNH | 0.5 per 50,000 persons; LSDP review of medicines for PNH (review summary and expert panel recommendations; October 2020 expert panel meeting). The submission assumed the prevalence rate to remain static over the initial 6 years of listing. | The full report was not available, and the underlying methodology/source of the estimate was unclear.  The submission assumed no growth in the underlying prevalence rate over time. The expert panel noted the number of patients requiring ongoing treatment for PNH is likely to continue to rise at a rate higher than population growth.  DUSC considered that there was some uncertainty in the estimate ofPNH but considered the prevalence estimate reasonable. |
| Proportion eligible for eculizumab | 77%; LSDP review of medicines for PNH (review summary and expert panel recommendations; October 2020 expert panel meeting). Approximately 63-77% of patients with PNH in Australia were estimated to be eligible for access to LSDP-subsidised treatment with eculizumab. | No justification was provided for the assumption of the higher end of the range. However, the estimated proportion may be reasonable given that the PBS restrictions for eculizumab and ravulizumab are slightly broader than the LSDP criteria (which excluded patients with severe aplastic anaemia).  DUSC considered that this figure was uncertain. |
| Proportion of eligible patients accessing PBS treatment | 100%; The submission assumed that all patients meeting the PBS eligibility criteria for the C5 inhibitors would be currently accessing PBS-subsidised eculizumab, ravulizumab or pegcetacoplan. The submission noted that the LSDP review suggested 53 to 84% of eligible patients with PNH were accessing a C5 inhibitor on the LSDP, but argued that this estimate did not include patients accessing treatment through clinical trials. | This assumption was considered uncertain, and may overestimate the proportion of patients currently on PBS treatment.  DUSC considered the assumption an overestimation when compared to current prescriptions of C5 inhibitors. |
| Proportion with inadequate response or intolerant to a C5 inhibitor | 43.9%; Based on the proportion of patients considered to be major responders (defined as transfusion independence and Hb ≥80 g/L and <110 g/L) in an observational study conducted by Risitano et al. (2009). | The submission’s estimate appeared to underestimate the proportion of patients with an inadequate response to a C5 inhibitor, as patients who were partial responders or minor responders (who would also be eligible for treatment with iptacopan) were not accounted for in the submission’s estimates.  The categories included in Risitano et al. did not appear to be applicable to the PBS population given that the proposed restriction does not include criteria relating to transfusion dependence, and is based on a Hb level <10.5 g/dL rather than <11 g/dL. Based on the data presented in Table 1 of Risitano et al., 21/41 (51.2%) had a Hb <10.5 g/dL while on treatment with eculizumab.  The sample size included in the study was relatively small and included a mix of continuing and newly treated patients treated with eculizumab (whereas the majority of patients in the PBS population are expected to be treated with ravulizumab).  The estimated proportion did not appear to account for patients who are intolerant to C5 inhibitor treatment.  DUSC considered that the proportion of patients with an inadequate response was overestimated. DUSC considered that the definition of responders was not clear and considered the proportion intolerant to C5 inhibitors to be around 19.5% as per Risitano et al., 2009. DUSC considered that the responder population should consist of both the optimal (36.6%) and major (43.9%) responders, while the intolerant population should consist of the partial (12.2%) and minor (7.3%) responders. |
| Patients on second-line treatment with pegcetacoplan in Year 1 who initiated prior to Year 1 | ||||1 patients. Assumption based on PBS dispensing data for pegcetacoplan to December 2023. The submission estimated that approximately ||||1 patients are currently receiving treatment with pegcetacoplan. | This number was considered uncertain due to the immaturity of the PBS dispensing data for pegcetacoplan.  DUSC considered that the patient numbers were overestimated relative to current C5 inhibitor prescriptions and relative to US estimates based on administrative data. |
| Uptake of second-line treatment | Yr 1: ||||%, Yr 2: ||||%, Yr 3: ||||%, Yr 4: ||||%, Yr 5: ||||%, Yr 6: ||||%. The submission argued that high uptake is expected for pegcetacoplan due to the unmet clinical need for second-line treatment for patients with suboptimal response to C5 inhibitor treatment, and given that pegcetacoplan allows for self-administration in the home setting. The submission argued that listing of iptacopan is not expected to increase the uptake of the second-line treatment overall. | The availability of an oral treatment is likely to increase the overall uptake of second-line treatment. However, it is unclear whether the assumed uptake rates will be realised given the relatively limited duration of effectiveness and safety data available for iptacopan and pegcetacoplan, particularly in relation to the occurrence of breakthrough haemolysis and major adverse vascular events (i.e., thrombosis).  DUSC considered that uptake estimates are higher than current practice for year 1 and are likely to be an overestimate. |
| Proportion of second-line initiators who elect treatment with iptacopan | ||||%. Assumption; the submission argued that the greater convenience of treatment with iptacopan (oral treatment) compared to pegcetacoplan (subcutaneous infusion) would result in an overall preference for iptacopan. | The evaluation considered the uptake rates were uncertain but may be reasonable given the convenience associated with an oral treatment compared to a twice weekly subcutaneous infusion.  DUSC considered that the uptake rate was reasonable given the mode of administration. |
| Proportion of second-line pegcetacoplan patients who switch to iptacopan | Y1 to Y3: ||||%, Y3 to Y6: ||||%. Assumption; the submission argued that the availability of an oral treatment would lead to the majority of patients switching to iptacopan during the initial 3 years. | The submission assumed that only 12.5% of patients (0.5 x 0.5 x 0.5) would remain on pegcetacoplan treatment after 3 years. While iptacopan provides a more convenient method of administration, patients may prefer to remain on pegcetacoplan if they are responding to pegcetacoplan therapy. Additionally, patients may be reluctant to switch from pegcetacoplan to iptacopan unless there is a clear path to allow reinitiation of treatment with pegcetacoplan in the case of iptacopan treatment failure/intolerance.  DUSC considered the estimates to be uncertain but reasonable given the mode of administration. |
| Second-line treatment discontinuation rate | ||||%. Assumption; based on the discontinuation rate of ||||% applied in the utilisation and financial implications for pegcetacoplan in the March 2022 submission for pegcetacoplan. | The underlying source of the discontinuation rate was unclear. Given the potential for complications associated with untreated PNH, patients who discontinue treatment are likely to switch to an alternative PNH treatment. While an annual discontinuation rate was incorporated, the submission’s estimates did not appear to account for patients who discontinue treatment due to not achieving a clinical improvement.  DUSC considered that applying this assumption was not necessary in a prevalent approach. |
| Patients initiating second-line treatment | Y1: ||||1, Y2: ||||1, Y3: ||||1, Y4: ||||1, Y5: ||||1, Y6: ||||1; Derived as the difference between the estimated total number of patients on second-line treatment in a particular year minus the number of patients continuing from previous years. | The number of patients initiating second-line treatment was dependent on the total number of patients on second-line treatment (based on the uptake rate assumed in the submission) and the rate of treatment discontinuation among patients on second-line treatment.  DUSC considered that given the uncertainties in the estimates used to derive this figure that it is itself uncertain and likely to be an overestimate. |
| Iptacopan and pegcetacoplan scripts per patient | 13 scripts per patient per year; Based on assumption of 52 weeks per year and one script every 4 weeks. | The calculation was based on 52 weeks (364 days) per year rather than 365.25 days, which underestimated the number of scripts per year.  DUSC considered that the compliance rate will be high but not necessarily 100%. However, the offset by the discontinuation rates was unnecessarily applied. |
| Ravulizumab scripts | 1 per initiating patient. The submission assumed that patients who move to second-line treatment and elect treatment with iptacopan would otherwise have initiated treatment with pegcetacoplan, which requires coadministration with a C5 inhibitor during the initial 4 weeks. Ravulizumab was used as a proxy for PBS listed C5 inhibitors (eculizumab and ravulizumab). | The submission’s estimates did not account for any rebates provided by the pegcetacoplan sponsor for the initial 4 weeks of treatment in which pegcetacoplan and ravulizumab are used concurrently.  DUSC considered that the estimated cost offsets due to pegcetacoplan having a four week period of coadministration with ravulizumab is unlikely to be realised due to existing rebates for these four weeks of treatment. |

Source: Section 4, of the submission; Section 4 utilisation and financial implications Excel workbook, Attachment 11 of the submission.

Abbreviations: Hb, haemoglobin; LSDP, Life Saving Drugs Program; PNH, paroxysmal nocturnal haemoglobinuria; Y, Year.

*The redacted values correspond to the following ranges:*

*1 < 500*

* 1. The estimated utilisation and financial implications of listing iptacopan (based on the estimated effective DPMQ) are presented in Table 17 based on the published prices of pegcetacoplan and ravulizumab.

Table 17: Estimated use and financial implications

|  | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
| --- | --- | --- | --- | --- | --- | --- |
| Estimated extent of use | | | | | | |
| Number of patients treated with iptacopan | |　1 | |　1 | |　1 | |　1 | |　1 | |　1 |
| Number of iptacopan scripts dispensed a | |　1 | |　1 | |　2 | |　2 | |　2 | |　2 |
| Cost to the PBS/RPBS (less copayments) | | | | | | |
| Cost of iptacopan to the PBS/RPBS | |　3 | |　3 | |　4 | |　4 | |　4 | |　4 |
| Cost offsets for reduced use of pegcetacoplan | |　5 | |　5 | |　5 | |　5 | |　5 | |　5 |
| Cost offsets for reduced use of ravulizumab | |　5 | |　5 | |　5 | |　5 | |　5 | |　5 |
| Net cost to PBS/RPBS | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 |
| Cost to the MBS | | | | | | |
| Cost of ravulizumab administration | |　5 | |　5 | |　5 | |　5 | |　5 | |　5 |
| **Net financial implications** | | | | | | |
| Net cost to the PBS/RPBS/MBS | |　6 | |　6 | |　6 | |　6 | |　6 | |　6 |

Source: Table 4-20,; Table 4-24 of the submission.

Abbreviations: MBS, Medicare Benefits Schedule.

a Derived based on 13 scripts per patient per year

*The redacted values correspond to the following ranges:*

*1 < 500*

*2 500 to < 5,0000*

*3 $10 million to < $20 million*

*4 $20 million to < $30 million*

*5 net cost saving*

*6 $0 to < $10 million*

* 1. The estimated net cost to the PBS/RPBS was $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, a total cost of $0 to < $10 million over the first 6 years of listing. The net cost was due to the higher drug cost for iptacopan compared to pegcetacoplan, resulting from the inclusion of cost offsets for 4 weeks of ravulizumab treatment in the cost-minimisation (despite ravulizumab treatment only being required in the first year of treatment with pegcetacoplan).
  2. DUSC considered the estimates presented in the submission to be high but uncertain. The main issues were:

DUSC noted that the epidemiology of PNH is not well characterised resulting in the estimates being uncertain.

DUSC considered that the estimates of C5 inhibitor failure based on major responders were an overestimate. DUSC considered that the intolerant population should consist of the partial and minor responders.

DUSC considers that patient numbers are overestimated relative to current C5 inhibitor prescriptions.

DUSC considers that the uptake rate is overestimated initially relative to pegcetacoplan uptake in year one.

Quality Use of Medicines

* 1. No quality use of medicines issues were raised in the submission, and no activities to support the quality use of medicines were proposed. Due to its relatively short half-life of 25 hours, patients treated with iptacopan may have a higher risk of breakthrough haemolysis compared to other available treatments if treatment is interrupted (i.e., due to treatment non-adherence). The pre-PBAC response stated that the sponsor plans to have educational material for doctors and nurses and a comprehensive patient support program to support the quality use of iptacopan.

Financial Management – Risk Sharing Arrangements

* 1. The submission noted that a cap-based risk sharing arrangement exists for pegcetacoplan and that the sponsor expects that iptacopan will be required to enter the same risk sharing arrangement.

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

1. PBAC Outcome
   1. The PBAC recommended the listing of iptacopan for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH) who have inadequate clinical response to Complement 5 (C5) inhibitor treatment. The recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of iptacopan would be acceptable if it were cost-minimised against pegcetacoplan, and included in the current Risk Sharing Arrangement for PNH.
   2. The PBAC noted the consumer comments from health care professionals and also during the sponsor hearing that described the benefits of iptacopan therapy targeting the alternative complement pathway (see paragraph 4.5) along with it being an oral therapy. The PBAC also acknowledged concerns raised by health care professionals regarding the potential for breakthrough haemolysis due to non-adherence with oral therapy and noted the sponsors plans for a comprehensive patient support program.
   3. With regard to the requested listing and restriction, the PBAC advised that:

Iptacopan can be administered outside of a hospital environment given it is an oral therapy with no additional monitoring requirements post administration stipulated in the TGA draft Product Information. As such, a general schedule listing rather than the requested Section 100 listing was appropriate.

An Authority Required (Written) listing was appropriate and noted that this was consistent with other PBS listing complement inhibitors for PNH.

The cautions outlined in paragraph 3.5 be included in the iptacopan restriction.

Unlike pegcetacoplan, combination treatment with a C5 inhibitor during the initial 4 weeks of iptacopan treatment is not required. As a result, the duration of the initial treatment phase of iptacopan should be increased to 6 months (i.e. 5 repeats) and the first and subsequent continuing treatment phases should be combined in one continuing treatment phase where the monitoring requirements only provided in the first continuing authority application similar to other PBS listings for PNH. In addition, the ‘initial treatment’ and the ‘return from PBS-subsidised eculizumab post pregnancy or from PBS-subsidised C5 inhibitor for reasons other than post pregnancy’ restrictions should include a clinical criterion specifying iptacopan must be the sole PBS subsidised treatment for this condition as iptacopan dosing doesn’t specify co-administration with a C5 inhibitor.

The proposed clinical criteria relating to inadequate response to a C5 inhibitor should be consistent with that of pegcetacoplan and specify a haemoglobin level of 105g/L (see paragraph 3.6).

Monitoring requirements along with the ‘return from PBS-subsidised eculizumab post-pregnancy or from PBS-subsidised C5 inhibitors for reasons other than post-pregnancy’ restriction should be consistent with pegcetacoplan. This will provide a path for patients who cease iptacopan temporarily in situations where they can’t take oral medications, e.g. for surgery reasons and wishes to come back to iptacopan.

Flow on changes to allow patients who develop resistance or intolerance to iptacopan to reinitiate treatment with eculizumab or ravulizumab were appropriate. Such flow on changes would also provide a path for patients who develop resistance or intolerance to iptacopan to switch from iptacopan to pegcetacoplan (see paragraph 3.7).

* 1. The PBAC considered that pegcetacoplan was appropriate as the main comparator.
  2. The PBAC noted the APPLY-PNH trial provided the key evidence for iptacopan. The PBAC agreed with the ESC that while the iptacopan trial (APPLY-PNH) had a high risk of bias, the majority of outcomes were objective and standard in PNH and advised that this was also the case for the pegcetacoplan trial (PEGASUS). The PBAC noted that the APPLY-PNH trial demonstrated statistically significant improvements in the primary outcomes (increase in haemoglobin level ≥2 g/dL and achievement of a haemoglobin level of ≥12 g/d) with iptacopan compared to treatment with a C5 inhibitor, for patients non-responsive to a C5 inhibitor. The PBAC noted that the improvements in the primary outcomes evident over the 24-week randomised treatment period were generally maintained over the extended follow-up to 48 weeks (in which patients in the iptacopan arm continued to receive iptacopan, and patients in the C5 inhibitor arm switched to iptacopan). The PBAC also noted that treatment with iptacopan was associated with a statistically significant improvement in FACIT-Fatigue score compared to treatment with a C5 inhibitor (mean difference: 8.29; 95% CI: 5.28, 11.29) and advised that the result represented a clinically important improvement (a difference of 5 points is considered clinically meaningful).
  3. The PBAC noted that no head-to-head trials comparing iptacopan and pegcetacoplan were identified and hence the clinical claim was based on a series of indirect comparisons. The PBAC considered the results of the Bucher method indirect comparisons and the matching adjusted indirect comparisons (MAIC) were highly uncertain as there were major differences between the iptacopan APPLY-PNH and pegcetacoplan PEGASUS trial (see paragraph 6.63). The PBAC noted similar uncertainty in trial data had previously been accepted for the pegcetacoplan submission. Acknowledging the transitivity concerns between the clinical trials the PBAC were satisfied that the clinically relevant outcomes were objective and demonstrated no significant differences using the Bucher method indirect comparison, anchored and unanchored MAICs. Overall, the PBAC agreed with the ESC that, in the context of this rare disease, it was reasonable to accept the claim of non-inferior effectiveness.
  4. The PBAC noted that in the APPLY-PNH trial over the 24-week randomised treatment period breakthrough haemolysis occurred in 3.2% of patients in the iptacopan arm compared to 17.1% of patients receiving a C5 inhibitor. Based on extended follow-up to 48 weeks there were 8 clinical breakthrough haemolysis events in 7 patients during iptacopan treatment, with an adjusted annualised clinical breakthrough haemolysis rate of 0.11 (95% CI: 0.05, 0.23). Acknowledging the methodological limitations of the comparison the PBAC noted that the matched and adjusted results for the unanchored MAIC found treatment with iptacopan was associated with a lower rate of serious adverse events compared to pegcetacoplan (see paragraph 6.60). The PBAC considered that the claim of non-inferior comparative safety was uncertain due to the relatively short duration of follow-up and the methodological limitations of the comparison but was reasonable in the context of this rare disease.
  5. The submission presented a cost-minimisation approach versus pegcetacoplan. The PBAC noted that the costs associated with the use of a C5 inhibitor during the initial 4 weeks of pegcetacoplan treatment were included in the cost-minimisation. The PBAC noted that iptacopan and pegcetacoplan are both chronic therapies and advised that a steady state dose comparison was therefore most relevant. As such, the PBAC considered that the costs associated with the use of a C5 inhibitor during the initial 4 weeks of pegcetacoplan treatment should not be included in the cost-minimisation. The PBAC noted that pegcetacoplan has a Section 100 listing whereas the Committee has proposed a Section 85 listing for iptacopan and that there are differences in supply chain costs between these two programs. The PBAC advised that the cost-minimisation account for any differences in supply chain costs such that the iptacopan ex-manufacturer price does not result in any additional cost to the PBS. In the absence of data on the proportion of patients who do not self-administer pegcetacoplan, the PBAC agreed with the exclusion of administration costs for pegcetacoplan in the CMA calculation (see paragraph 6.77). The PBAC considered the following equi-effective doses appropriate (based on 365 days):

Iptacopan 146,048 mg (200 mg/capsule × 56 capsules/pack × 13.04 packs) is equivalent to pegcetacoplan 116,365 mg (1,080 mg/vial × 107.7 injections).

* 1. The PBAC agreed with the DUSC that the financial estimates based on the epidemiological approach were high and uncertain. The PBAC considered that while there was some uncertainty in the estimates of PNH the prevalence estimate used in the financial estimates was reasonable. The PBAC agreed with the DUSC that the proportion of patients with an inadequate response or intolerant to a C5 inhibitor was overestimated and considered it should be reduced from 43.9% to 19.5% (see Table 16). The PBAC agreed with the DUSC that the uptake of second-line treatment estimates were higher than current practice for year 1 and are likely to be an overestimate and advised a reduction based on current pegcetacoplan prescription numbers. It was noted there were 18 continuing prescriptions dispensed for pegcetacoplan in January 2024. The PBAC considered that the estimated cost offsets due to pegcetacoplan having a four week period of coadministration with ravulizumab are unlikely to be realised due to existing rebates for this period. The PBAC advised that the financial estimates would need to be revised to account for existing rebates when establishing cost offsets, use an input of 19.5% for the proportion of patients with an inadequate response or intolerant to a C5 inhibitor and amend year 1 uptake rates for second-line treatment estimates. The PBAC considered it was appropriate for iptacopan to be cost neutral to the PBS.
  2. The PBAC noted that a risk sharing arrangement exists for pegcetacoplan and considered it appropriate that that iptacopan enter the same risk sharing arrangement with no increase to the caps.
  3. The PBAC recommended that iptacopan should not be treated as interchangeable with any drugs.
  4. The PBAC advised that iptacopan is not suitable for prescribing by nurse practitioners.
  5. The PBAC recommended that the Early Supply Rule should not apply.
  6. The PBAC noted that flow on changes to the restriction criteria for eculizumab, ravulizumab and pegcetacoplan would be required as per paragraphs 8.2 to 8.5.
  7. The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because iptacopan is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over pegcetacoplan, 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.
  8. The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

1. Recommended listing
   1. Add new item:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 [new 1] / Treatment of Concept: [new 2]** | | | | | | | |
|  | | **Category / Program:** S85 General schedule (code: GE) | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required – In Writing/HPOS | | | | | |
| 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:**  Complement 5 (C5) inhibitors are defined as eculizumab or ravulizumab | | | | | |
|  | **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  Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos  Or mailed to:  Services Australia  Complex Drugs  Reply Paid 9826  HOBART TAS 7001 | | | | | |
|  | **Administrative Advice:**  No increase in the maximum quantity or number of units may be authorised. | | | | | |
|  | **Administrative Advice:**  No increase in the maximum number of repeats may be authorised. | | | | | |
|  | | **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 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 the sole PBS subsidised treatment 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:  (1) details of the proposed prescription; and  (2) 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) | | | | | |
|  | | | | | | | |
| **Restriction Summary [new 3] / Treatment of Concept: [new 4]** | | | | | | | |
|  | | **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) | | | | | |
|  | | **Treatment Phase:** Return from PBS-subsidised eculizumab post pregnancy or from PBS-subsidised Complement 5 (C5) inhibitor for reasons other than post pregnancy | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have received prior PBS-subsidised treatment with this drug for this condition, | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have received prior PBS-subsidised treatment with eculizumab through the 'Initial treatment - Initial 3 (switching from PBS-subsidised pegcetacoplan or iptacopan for pregnancy (induction doses)' criteria; OR | | | | | |
|  | | Patient must have received prior PBS-subsidised treatment with at least one C5 inhibitor and returning to iptacopan treatment for reasons other than post pregnancy, | | | | | |
|  | | **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 be the sole PBS subsidised treatment 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:  (1) details of the proposed prescription; and  (2) 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**:  Patients may qualify under this treatment phase more than once. | | | | | |
| **Restriction Summary [new 5] / Treatment of Concept: [new 6]** | | | | | | | |
|  | | | | | | | |
|  | | **Indication:** Paroxysmal nocturnal haemoglobinuria (PNH) | | | | | |
|  | | **Treatment Phase:** Continuing treatment | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have received PBS-subsidised treatment with this drug for this condition | | | | | |
|  | | **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 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:  (1) details of the proposed prescription; and  (2) 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 on the first continuing authority application:  (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) | | | | | |
|  | | | | | | | |
|  | | **Indication**: Paroxysmal nocturnal haemoglobinuria (PNH) | | | | | |
|  | | **Treatment Phase**: Transitioning from non-PBS to PBS subsided treatment – ‘Grandfather’ arrangement | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to (insert PBS listing date), | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have a documented PNH granulocyte clone size equal to or greater than 10% within the 3 months prior to initiating non-PBS-subsidised treatment with this drug, | | | | | |
|  | | **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 prior to initiating non-PBS-subsidised treatment with this drug; OR | | | | | |
|  | | Patient must be intolerant to C5 inhibitors as determined by the treating physician prior to initiating non-PBS-subsidised treatment with this drug, | | | | | |
|  | | **AND** | | | | | |
|  | | **Clinical criteria:** | | | | | |
|  | | Patient must have been receiving treatment with at least one C5 inhibitor for at least 3 months prior to 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 the sole PBS-subsidised therapy for this condition. | | | | | |
|  | | **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 | | | | | |
|  | | **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:  (1) details of the proposed prescription; and  (2) 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) | | | | | |
|  | | **Administrative advice**: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. | | | | | |
|  | | **Administrative advice**: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. | | | | | |

* 1. Flow on changes to ravulizumab and eculizumab to allow:

1- switching from PBS subsidised iptacopan to eculizumab for pregnancy (induction doses)

2- return to one of C5 inhibitors (induction doses) for patients who are intolerant/resistant to iptacopan.

Additions are in italics and deletions are in strikethrough.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **Medicinal Product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of  Rpts** | **Available brands** |
| eculizumab 300 mg/ 30 mL injection, 30 mL vial | 12840T (Public)  12896R (Private) | 8 | 8 | 0 | Soliris |

|  |  |
| --- | --- |
| **Edit of Restriction Summary 13458 / ToC: 13458: Authority Required** | |
|  |  |
|  | **Indication:**  Paroxysmal nocturnal haemoglobinuria (PNH) |
|  | **Treatment Phase:** Initial treatment –(initial 3) switching from PBS-subsidised pegcetacoplan *or iptacopan* for pregnancy (induction doses) |
|  |  |
|  | **Clinical criteria:** |
|  | Patient must be planning pregnancy; or |
|  | Patient must be pregnant |
|  |  |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have received PBS-subsidised treatment with *either (i)* pegcetacoplan, *(ii) iptacopan* for this condition |
|  |  |
|  | **AND** |
|  | **Clinical criteria:** |
|  | ~~The treatment must not be in combination~~ *~~with either of (i) ravulizumab, (ii) pegcetacoplan~~*  *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 |
|  |  |
|  | **Prescribing Instructions:**  ~~The authority application must be made in writing and must include:~~  ~~(1) a completed authority prescription form; and~~  ~~(2) 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).~~  *The authority application must be made in writing and must include:*  *(1) details of the proposed prescription; and*  *(2) 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:**  Patient may qualify under this treatment phase more than once. In the event of miscarriage, patient may continue on eculizumab if patient is stable, and/or is planning a subsequent pregnancy. For continuing PBS-subsidised treatment, a ‘Switching’ patient must proceed under the 'Subsequent Continuing Treatment' criteria. |
|  | |
| **Edit of Restriction Summary 13460 / ToC: 13459: Authority Required** | |
|  |  |
|  | **Indication:**  Paroxysmal nocturnal haemoglobinuria (PNH) |
|  |  |
|  | **Treatment Phase:** 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) inhibitorfor 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 not be in combination with either of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan~~  *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 |
|  |  |
|  | **Prescribing Instructions:**  ~~The authority application must be made in writing and must include:~~  ~~(1) a completed authority prescription form; and~~  ~~(2) 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).~~  *The authority application must be made in writing and must include:*  *(1) details of the proposed prescription; and*  *(2) 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:**  For continuing PBS-subsidised treatment with this drug, a 'Returning' patient must proceed under the ‘Subsequent Continuing Treatment' criteria. |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **Medicinal Product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of  Rpts** | **Available brands** |
| ravulizumab 1.1 g/11 mL injection, 11 mL vial | 12856P (Public)  12901B (Private) | 1 | 1 | 0 | Soliris |
| ravulizumab 300 mg/3 mL injection, 3 mL vial | 12898W (Public)  12841W (Private) | 1 | 1 | 0 | Soliris |

|  |  |
| --- | --- |
| **Edit of Restriction Summary 14533 / ToC: 14477: Authority Required** | |
|  |  |
|  | **Indication:**  Paroxysmal nocturnal haemoglobinuria (PNH) |
|  |  |
|  | **Treatment Phase:** Return from PBS subsidised pegcetacoplan *or iptacopan*– induction dose |
|  |  |
|  | **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 not be in combination with either of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan~~  *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 |
|  |  |
|  | **Prescribing Instructions:**  ~~The authority application must be made in writing and must include:~~  ~~(1) a completed authority prescription form; and~~  ~~(2) 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).~~  *The authority application must be made in writing and must include:*  *(1) details of the proposed prescription; and*  *(2) 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:**  For continuing PBS-subsidised treatment with this drug, a 'Returning' patient must proceed under the ‘Subsequent Continuing Treatment' criteria. |

* 1. Flow on changes to pegcetacoplan to allow patients returning to pegcetacoplan for reasons other than post pregnancy from one of the PBS-listed therapies for PNH, including iptacopan. Additions are in italics and deletions are in strikethrough.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **Medicinal Product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№. of  Rpts** | **Available brands** |
| pegcetacoplan 1.08 g/20 mL injection, 20 mL vial | 13175K (Public)  13191G (Private) | 1 | 1 | 0 | Empaveli |

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| --- | --- |
| **Edit of Restriction Summary 13659 / ToC: 13710: Authority Required** | |
|  |  |
|  | **Indication:**  Paroxysmal nocturnal haemoglobinuria (PNH) |
|  |  |
|  | **Treatment Phase:** Return from PBS-subsidised eculizumab post pregnancy or from *one of the* PBS-subsidised ~~Complement 5 (C5) inhibitor~~ *therapies for this condition*, for reasons other than post pregnancy |
|  |  |
|  | **Clinical criteria:** |
|  | Patient must have received prior PBS-subsidised treatment with this drug for this condition |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have received prior PBS-subsidised treatment with eculizumab through the Initial treatment - Initial 3 (switching from PBS-subsidised pegcetacoplan for pregnancy (induction doses) criteria; or |
|  | Patient must have received prior PBS-subsidised treatment with at least one ~~C5 inhibitor~~ *drug listed for this condition* and returning to pegcetacoplan treatment for reasons other than post pregnancy |
|  | **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 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:~~  ~~(1) a completed authority prescription form; and~~  ~~(2) 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).~~  *The authority application must be made in writing and must include:*  *(1) details of the proposed prescription; and*  *(2) 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) |
|  | **Prescribing Instructions:**  For the purposes of family planning, patient may qualify under this treatment phase more than once. To return to pegcetacoplan treatment for reasons other than post pregnancy, patient may qualify under this treatment phase once only in any 12 consecutive months. Where long-term continuing PBS-subsidised treatment with pegcetacoplan is planned, a 'Returning' patient must proceed under the 'Subsequent Continuing Treatment' criteria of pegcetacoplan. |

* 1. Flow on changes to the following ravulizumab, eculizumab and pegcetacoplan restrictions for PNH:

Item codes: Eculizumab : 12840T, 12864C, 12877R, 12896R, 12899X, 12900Y

Item codes: Ravulizumab: 12856P, 12883C, 12897T, 12901B, 12841W, 12884D, 12895Q, 12898W

Item codes: Pegcetacoplan: 13185Y, 13197N (first and subsequent continuing treatment phases)

to change the clinical criterion Concept ID: 29991 and 29988 to avoid further addition of medicines’ names as they get recommended for PNH. The concepts will change from either:

|  |  |
| --- | --- |
|  | ~~The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan~~ |

|  |  |
| --- | --- |
|  | ~~The treatment must not be in combination with a Complement 5 (C5) inhibitor~~ |

**to:**

|  |  |
| --- | --- |
|  | *The treatment must be the sole PBS-subsidised therapy for this condition.* |

* 1. Flow on changes to all ravulizumab, eculizumab and pegcetacoplan restrictions for PNH:

Item codes: Eculizumab : 12840T, 12864C, 12877R, 12896R, 12899X, 12900Y

Item codes: Ravulizumab: 12856P, 12883C, 12897T, 12901B, 12841W, 12884D, 12895Q, 12898W

Item codes: Pegcetacoplan: 13196M, 13191G, 13180Q, 13175K, 13185Y, 13197N

change in concept ID: 27164 that includes completed authority prescription form(s);

to concept ID: 32530 that includes details of the proposed prescription.

|  |  |
| --- | --- |
|  | **Prescribing Instructions:**  ~~The authority application must be made in writing and must include:~~  ~~(1) a completed authority prescription form; and~~  ~~(2) 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).~~  *The authority application must be made in writing and must include:*  *(1) details of the proposed prescription; and*  *(2) 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).* |

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

1. **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.

1. **Sponsor’s Comment**

The sponsor had no comment.