6.04 RAVULIZUMAB, Solution concentrate for I.V. infusion 300 mg in 3 mL, Solution concentrate for I.V. infusion 1,100 mg in 11 mL, Ultomiris®, Alexion Pharmaceuticals Australasia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH).

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus eculizumab. A claim of non-inferiority was made in the submission based on an unanchored (naïve) indirect comparison between two single-arm studies.

1.3 The rationale provided in the submission was based on the following:

- the only registered treatments capable of changing the course of PNH in the paediatric population are the Complement 5 (C5) inhibitors, eculizumab and ravulizumab; and
- there is an unmet clinical need for a tolerated and equally effective therapy, with the potential to ease the treatment burden associated with eculizumab treatment in PNH.

1.4 Table 1 summarises the components of the overall clinical claim addressed by the submission.

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

<table>
<tr><th>Component</th><th>Description</th></tr>
<tr><td>Population</td><td>Paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH).</td></tr>
<tr><td>Intervention</td><td>Ravulizumab: The recommended dosing regimen consists of a loading dose followed by maintenance dosing at a once every 8-week (≥20 kg) or 4-week (<20 kg) interval, starting 2 weeks after loading dose administration.
Doses are administered by intravenous infusion based on the patient's body weight, as shown below.
<table>
<tr><th>Body weight range (kg)</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)</th><th>Dosing interval</th></tr>
<tr><td>≥5 to <10 kg</td><td>600</td><td>300</td><td>Every 4 weeks</td></tr>
<tr><td>≥10 to <20</td><td>600</td><td>600</td><td>Every 4 weeks</td></tr>
<tr><td>≥20 to <30</td><td>900</td><td>2,100</td><td>Every 8 weeks</td></tr>
<tr><td>≥30 to <40</td><td>1,200</td><td>2,700</td><td>Every 8 weeks</td></tr>
<tr><td>≥40 to <60</td><td>2,400</td><td>3,000</td><td>Every 8 weeks</td></tr>
<tr><td>≥60 to <100</td><td>2,700</td><td>3,300</td><td>Every 8 weeks</td></tr>
<tr><td>≥100</td><td>3,000</td><td>3,600</td><td>Every 8 weeks</td></tr>
</table>
For patients switching from eculizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, followed by maintenance doses starting 2 weeks after loading dose administration as per directions above.</td></tr>
<tr><td>Comparator</td><td>Eculizumab: The recommended dosing regimen in patients ≥ 40 kg consists of an initial phase comprising 900 mg weekly intravenous infusions for 4 weeks followed by a maintenance phase of 1200 mg intravenous infusions every 14 days, starting in the fifth week. For patients < 40 kg, the initial and maintenance phase doses are weight-dependent, as outlined below.
<table>
<tr><th>Body weight range (kg)</th><th>Initial phase</th><th>Maintenance phase</th></tr>
<tr><td>5 to <10</td><td>300 mg week 1</td><td>300 mg week 2; then 300 mg every 3 weeks</td></tr>
<tr><td>10 to <20</td><td>600 mg week 1</td><td>300 mg week 2; then 300 mg every 2 weeks</td></tr>
<tr><td>20 to <30</td><td>600 mg weeks 1 and 2</td><td>600 mg week 3; then 600 mg every 2 weeks</td></tr>
<tr><td>30 to <40</td><td>600 mg weeks 1 and 2</td><td>900 mg week 3; then 900 mg every 2 weeks</td></tr>
<tr><td>≥40</td><td>900 mg weeks 1, 2, 3 and 4</td><td>1,200 mg week 5; then 1200 mg every 2 weeks</td></tr>
</table></td></tr>
<tr><td>Outcomes</td><td>(i) Transfusion avoidance: proportion of patients who remain transfusion-free and do not require a transfusion (as per protocol) through Day 183 (Week 26)
(ii) Percentage change in LDH and free haemoglobin from baseline to Day 183 (Week 26)
(iii) Change in QoL (FACIT Fatigue questionnaire score) from baseline to Day 183 (Week 26)
(iv) Proportion of patients with stabilised haemoglobin: avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Week 26
(v) Proportion of patients with BTH: at least one new or worsening symptom or sign of intravascular haemolysis[a] in the presence of elevated LDH as follows:
• For patients who enter the study naïve to complement inhibitor treatment, elevated LDH ≥ 2 x ULN after prior LDH reduction to < 1.5 x ULN on therapy
• For patients who enter the study stabilised on eculizumab treatment, elevated LDH ≥ 2 x ULN</td></tr>
<tr><td>Clinical claim</td><td>Ravulizumab is non-inferior in terms of efficacy and safety and has a reduced treatment burden relative to eculizumab.</td></tr>
</table>

Source: Table 1.1, pp15-16 of the submission

BTH=breakthrough haemolysis; FACIT=Paediatric Functional Assessment of Chronic Illness Therapy; LDH=lactate dehydrogenase; QoL= quality of life; ULN=upper limit of normal

[a] Fatigue, hemoglobinuria, abdominal pain, shortness of breath, anaemia, major adverse vascular events, dysphagia, or erectile dysfunction.

2 Background

Registration status

2.1 The TGA approved ravulizumab 10 mg/mL (300 mg in 30 mL) for the treatment of adult patients with PNH on 17 October 2019. An application to register an additional strength of 100 mg/mL (1,100 mg in 11 mL) was approved on 25 March 2021.

2.2 In August 2022, TGA approved ravulizumab for the treatment of atypical Haemolytic Uraemic Syndrome (aHUS) and paediatric patients with PNH.

2.3 In the United States, ravulizumab is approved for the treatment of adult and paediatric patients one month of age and older with PNH. In the European Union (EU) and the United Kingdom, ravulizumab is approved for the treatment of adult and paediatric patients with a body weight of ≥ 10 kg with PNH.

Previous PBAC consideration

2.4 This is the first submission to the PBAC for consideration of ravulizumab to treat paediatric patients with PNH.

2.5 At the July 2020 PBAC meeting, the PBAC did not recommend ravulizumab for the treatment of adult patients (age ≥ 18 years) with PNH. Although the PBAC considered that ravulizumab was likely non-inferior to eculizumab in the short-term, there was a lack of long-term follow-up data (paragraph 7.1, ravulizumab, Public Summary Document (PSD), July 2020 PBAC meeting).

2.6 At the July 2020 PBAC meeting, the Committee noted that unlike eculizumab, which was indicated for use in both children and adults, the TGA approved indication and requested restriction for ravulizumab limited treatment to adults, as safety and efficacy data in children with PNH had not been established (paragraph 4.4, ravulizumab, PSD, July 2020 PBAC meeting).

2.7 Ravulizumab was subsequently recommended by the PBAC (under the Section 100 – Highly Specialised Drugs Program) for the treatment of PNH in adults (July 2021 meeting) and is currently reimbursed via the PBS. The PBAC considered that ravulizumab was likely to be non-inferior in safety and effectiveness compared to eculizumab (paragraph 7.1, ravulizumab, PSD, July 2021 PBAC meeting). At the time of the July 2021 PBAC meeting, ravulizumab had not yet received TGA approval for use in the paediatric population.

2.8 The PBAC noted that eculizumab was funded on the Life Saving Drugs Program (LSDP) at the time of the July 2021 PBAC meeting. Although the magnitude of the survival benefit in PNH remained uncertain and the cost-effectiveness was very high, the PBAC considered eculizumab would be appropriate for inclusion on the PBS with a price reduction. The PBAC advised ravulizumab be listed based on a cost-minimisation to eculizumab at the reduced price (paragraphs 7.1-7.3, ravulizumab, PSD, July 2021 PBAC meeting).

2.9 In the July 2021 ravulizumab resubmission, the PBAC advised that the CMA analysis should be based on: i) the eculizumab price established following the outcomes of its considerations; ii) administration costs for standard specialist follow-up consultation MBS item 105; and iii) a two-year period from initiation of treatment, for consistency with other drugs which include a loading dose in year one. The PBAC considered the estimated equi-effective doses over the first two years of treatment were ravulizumab 44,616 mg (13.75 infusions including loading dose) and eculizumab 47,400 mg (54 infusions) (paragraph 7.15, ravulizumab, PSD, July 2021 PBAC meeting).

2.10 The PBAC considered that a Risk Sharing Arrangement (RSA) was appropriate to manage any residual uncertainty associated with the cost to government of listing eculizumab and ravulizumab on the PBS, consistent with arrangements that currently apply to eculizumab under the Deed for supply through the LSDP. The PBAC also recommended that ravulizumab should be treated as interchangeable on an individual patient basis with eculizumab (paragraphs 7.17-7.18, ravulizumab, PSD, July 2021 PBAC meeting).

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed price for Max. Qty Published price (effective price)	Max. qty packs	Max. qty units	№. of Rpts	Available brands
RAVULIZUMAB					
Ravulizumab 300 mg/3 mL injection, 3 mL vial	Public hospital: $6,574.12 ($[redacted]) Private hospital: $6,621.94 ($[redacted])	1	1	2	Ultomiris
Ravulizumab 1.1 g/11 mL injection, 11 mL vial	Public hospital: $24,105.11 ($[redacted]) Private hospital: $24,152.93 ($[redacted])	1	1	2	Ultomiris
Proposed PBS restriction: initiation for complement inhibitor-naïve patients with PNH					
Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required – written					
Episodicity: Not applicable					
Severity: Not applicable					
Condition: Paroxysmal nocturnal haemoglobinuria (PNH)					
Treatment Phase: Initial treatment- Initial 1 (new patient)					
Restriction: Authority Required - written					
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					
Clinical criteria:					
Patient must not have received prior treatment with this drug for this condition, AND					
Patient must have a diagnosis of PNH established by flow cytometry, AND					
Patient must have a PNH granulocyte clone size equal to or greater than 10%, AND					
Patient must have a raised lactate dehydrogenase value at least 1.5 times the upper limit of normal, AND					
Patient must have experienced a thrombotic/embolic event which required anticoagulant therapy; OR					

Patient must have been transfused with at least 4 units of red blood cells in the last 12 months, OR
Patient must have chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple haemoglobin measurements not exceeding 70 g/L in the absence of anaemia symptoms; OR
Patient must have chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple red blood cell measurements not exceeding 100 g/L in addition to having anaemia symptoms; OR
Patient must have debilitating shortness of breath/chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded; OR
Patient must have a history of renal insufficiency, demonstrated by an eGFR less than or equal to 60 mL/min/1.73m^2, where causes other than PNH have been excluded; OR
Patients must have recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded, AND
The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan
~~**Population criteria**: Patient must be at least 18 years of age.~~
Prescribing instructions: At the time of the authority application, medical practitioners should request the appropriate number of vials, to provide for a single infusion to cover the loading dose and maintenance doses based on the patient's weight and as per the Product Information. Refer to the Product information for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1100 mg in 11 mL vials).
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. EST 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 No increase in the maximum number of repeats may be authorised
Caution: WARNING: This drug increases the risk of meningococcal infections (sepsis and/or meningitis). Consult the approved PI for information about vaccination against meningococcal infection.

Requested restriction for ravulizumab –for patients transitioning from eculizumab to ravulizumab (abridged)
Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private)
Condition: Paroxysmal nocturnal haemoglobinuria
PBS indication: Paroxysmal nocturnal haemoglobinuria
Restriction type: ☒Authority Required – written
Treatment Phase: Initial treatment- Initial 2 (switching from eculizumab)
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
Clinical criteria:
Patient must have previously received eculizumab for the treatment of this condition funded under the Australian Government's Life Saving Drugs Program (LSDP), OR
Patient must have received prior PBS-subsidised treatment with this drug for this condition; AND

Patient must have a diagnosis of PNH established by flow cytometry prior to LSDP-funded treatment with eculizumab, AND received prior PBS-subsidised treatment with eculizumab through the 'Initial treatment - Initial 2 (switching from PBS-subsidised ravulizumab for pregnancy)' criteria; AND
The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan
~~**Population criteria**: Patient must be at least 18 years of age.~~

Requested restriction for ravulizumab – continuing treatment
Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private)
PBS indication: Paroxysmal nocturnal haemoglobinuria
Restriction type: ☒Authority Required – written
Treatment Phase: continuing treatment
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
Clinical criteria:
First Continuing Criteria: Patient must have received PBS-subsidised treatment with this drug for this condition under the 'Initial' or 'Grandfather' treatment restriction, AND The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan. Subsequent Continuing Treatment: Patient must have previously received PBS-subsidised treatment with this drug for this condition under the 'First Continuing Treatment' or 'Return' criteria, AND 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 The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan.
~~**Population criteria**: Patient must be at least 18 years of age.~~

The submission requested an amendment to the existing 'Population criteria' for ravulizumab on the PBS that removes the criterion of a patient being at least 18 years of age (as indicated in red strikethrough text).

3.1 The submission stated that:

- due to international price referencing concerns, the sponsor required the existing Special Pricing Arrangement (SPA) to remain upon the expansion to the listing of ravulizumab on the PBS to include both adult and paediatric PNH patients; and
- no changes were proposed to the existing RSA established prior to the listing of eculizumab and ravulizumab on 1 March 2022 for the treatment of PNH and amended on 1 December 2022 to include pegcetacoplan.

3.2 A SPA and RSA apply to i) eculizumab: PNH - intravenous (IV) infusion 300 mg in 30 mL = $ (pricing quantity (PQ) = 1), and ii) ravulizumab: PNH – IV infusion 300 mg in 3 mL = $ (PQ = 1); PNH - IV infusion 1,100 mg in 11 mL = $ (PQ = 1).

3.3 The submission requested an amendment to the existing 'Population criteria' for ravulizumab on the PBS – to remove the criterion of a patient being at least 18 years of age.

3.4 The assessment and monitoring requirements for determining patient eligibility for initial or continuing treatment were unchanged from the existing PBS eligibility criteria

for treatment with eculizumab and ravulizumab. The requested restriction for ravulizumab allows for patients transitioning from eculizumab to ravulizumab.

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

4 Population and disease

4.1 PNH is a rare, life-threatening condition that can occur at any age but is most often diagnosed in young adults 30 to 40 years of age. It occurs due to an acquired mutation in the phosphatidylinositol glycan A (*PIG-A*) gene which results in a lack of terminal complement inhibitor proteins on cell surfaces. Their absence in blood cells results in uncontrolled complement activation and systemic complications which include chronic intravascular haemolysis, impaired bone marrow function, and thrombosis. Thromboembolic events are the leading cause of death in patients with PNH.

4.2 The severity of PNH is variable and not all patients require active complement inhibitor therapy. Patients with less severe disease can be treated with supportive therapies including folic acid and iron tablets; while patients with more severe disease may require red blood cell transfusions and anticoagulants. Life-long treatment is usually required. There is potential for cure with allogeneic stem cell transplantation; but this is rarely used as it is associated with a high level of morbidity and mortality (paragraph 4.2, ravulizumab, PSD, July 2021 PBAC meeting).

4.3 Patients with classic PNH had a significant reduction in age-specific life expectancy. Prognosis is likely to change over time, with differences in risk of thromboembolic events and mortality among subtypes of PNH (classic PNH, aplastic anaemia PNH, and intermediate PNH). Paediatric cases of PNH account for 5–10% of reported cases of PNH (Delegate's Overview for ravulizumab, PM-2021-01659-1-6). The submission noted that as of October 2022, PBS service data indicated that a total of 152 PNH patients were on treatment with either eculizumab or ravulizumab, of whom only two patients were < 18 years old and were being treated with eculizumab.

4.4 Ravulizumab, a long-acting anti-C5 monoclonal antibody that antagonises terminal complement at the same C5 epitope as eculizumab, is administered as a weight-based dose via IV infusion. The regimen starts with a loading dose, followed by maintenance dosing (every 4 weeks for body weight ≥ 5 to < 20 kg and every 8 weeks for body weight ≥ 20 kg) as per Table 1, and therefore has a lower treatment burden (less frequent dosing) than eculizumab (dosing every 3 weeks for body weight 5 to < 10 kg and every 2 weeks for body weight ≥ 20 kg).

4.5 Ravulizumab has not been studied in PNH patients who weigh < 30 kg. The dosing regimen to be used in paediatric patients with PNH who weigh < 30 kg is identical to the weight-based dosing recommendations provided for paediatric patients with aHUS based on pharmacokinetic/pharmacodynamic (PK/PD) data available in aHUS/PNH patients treated with ravulizumab. The efficacy and safety profile in paediatric patients with body weight ≥5 kg is expected to be similar to that of adults (p5, TGA approved Product Information (PI) for ravulizumab).

4.6 Similar to eculizumab, the PI for ravulizumab contains a boxed warning regarding the risk of meningococcal infections and recommendations for vaccination and monitoring. Patients must be administered a meningococcal vaccine at least two weeks prior to the first dose of ravulizumab unless the risks of delaying ravulizumab therapy outweigh the risk of developing a meningococcal infection. Patients who initiate ravulizumab treatment less than two weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until two weeks after vaccination).

4.7 Ravulizumab is positioned as an alternative treatment to eculizumab for paediatric patients with PNH. Patients with PNH who do not meet the criteria for subsidised treatment with eculizumab or ravulizumab receive symptomatic treatment with best supportive care (BSC), such as transfusion of red blood cells, iron/folic acid therapy, steroids, anticoagulants, and immunosuppressive therapies.

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

5 Comparator

5.1 The submission nominated eculizumab as the comparator. This was appropriate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

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

Clinical studies

6.3 The submission was based on an unanchored indirect comparison using the key single arm study of ravulizumab (Study 304) and a single arm study of eculizumab (M07-005).

6.4 Study 304 included a complement inhibitor treatment-naïve cohort (n=4) and an eculizumab-experienced cohort (n=8). Study M07-005 only included complement inhibitor treatment-naïve patients (n=7).

6.5 The indirect comparison approach taken by the submission was as follows:

- Complement inhibitor treatment-naïve patients: The treatment-naïve cohort from Study 304 (n=4) was compared with the whole study population from the eculizumab study M07-005 (complement inhibitor treatment-naïve population, n=7).
- Eculizumab-experienced patients: In Study 304, eight patients switched from eculizumab to ravulizumab at baseline. As study M07-005 did not include

complement treatment-experienced patients, the submission presented a 'before and after' comparison of the eculizumab-experienced cohort in Study 304 (n=8) to inform the efficacy and safety of ravulizumab in patients who switch from eculizumab.

6.6 Details of the studies presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Single arm study of ravulizumab in paediatric patients with PNH		
Study 304	CSR ALXN1210-PNH-304. A Phase 3, Open-Label Study of ALXN1210 in Children and Adolescents with Paroxysmal Nocturnal Hemoglobinuria (PNH) Poster. Pharmacokinetics, pharmacodynamics, efficacy and safety of ravulizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria: interim analysis of a phase 3, open-label study. European Hematology Association (EHA) Poster number EP590, Virtual.	September 2020 June 9–17, 2021
Single arm study of eculizumab in paediatric patients with PNH		
Study M07-005	CSR M07-005. An Open-Label Multi-Center Study of Eculizumab in Children and Adolescents with a Diagnosis of Paroxysmal Nocturnal Hemoglobinuria Reiss, UM, et al. Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria.	March 2012 *Pediatric blood & cancer* 2014*;* 61(9), 1544–1550

Source: Table 4, Section 1.2.3, Clinical Overview, Attachment 2 accompanying the submission.
PNH = Paroxysmal Nocturnal Haemoglobinuria

6.7 A summary of the characteristics of the included studies is presented in Table 3.

Table 3: Summary of key characteristics of the studies included in the submission

	Ravulizumab study	Eculizumab study
	Study 304 (NCT03406507)	**Study M07-005 (NCT00867932)**
N	12	7
Period conducted	Start: February 2018 Data cutoff: March 2020	Start: October 2009 Data cutoff: May 2011
Design	Open-label, single-arm, multicentre/multinational	Post-marketing, single-arm multicentre
Population	Paediatric patients (< 18 years of age) with PNH	Paediatric patients (2 - 17 years of age) with PNH
Treatment duration	Primary evaluation: 26 weeks. Extension period: until the product is registered or approved (in accordance with country-specific regulations) or for up to 4 years whichever occurs first.	12 weeks.
Primary endpoint	PK/PD parameters (trough and peak) at baseline and Weeks 2, 10, 18, and 26	PK/PD parameters (trough and peak) at Baseline and Weeks 6 and 12
Key secondary or other endpoints	Change in LDH, plasma-free haemoglobin, and QoL from baseline to Week 26 (Day 183). Transfusion avoidance Proportion of patients with stabilised haemoglobin Proportion of patients with BTH Safety	Change in LDH from baseline to Week 12 Change in plasma-free haemoglobin from Baseline to Week 12 Change in QoL PNH clone size Safety

Source: Table 2.1, p33 of the submission.
BTH=breakthrough haemolysis; LDH=lactate dehydrogenase; PD=pharmacodynamic; PNH=Paroxysmal Nocturnal Hemoglobinuria; PK=pharmacokinetic; QoL=quality of life

6.8 Study 304 included patients aged < 18 years and weighing ≥ 5 kg (in line with the minimum weight as per the dosing recommendations for ravulizumab in the PI). Study M07-005 included patients between 2 to 17 years of age, with no weight-based requirement.

6.9 Study 304 required patients to have a lactate dehydrogenase (LDH) level ≥ 1.5 × upper limit of normal (ULN) at baseline (consistent with the requested restriction); whereas in Study M07-005, patients must have an LDH level > ULN or at least one transfusion in the past two years for anaemia-related symptoms.

6.10 Study 304 excluded patients with platelet count < 30×10^9/L and absolute neutrophil count < 0.5×10^9/L; Study M07-005 did not exclude patients based on these parameters. In Study 304, concomitant use of anticoagulants was prohibited for patients not on a stable regimen for at least two weeks prior to Day 1; this was not a requirement in Study M07-005.

6.11 A comparison of baseline characteristics between the studies is not reliable given the small number of enrolled patients and should be interpreted in the context of the rarity of PNH in the paediatric population.

6.12 The submission stated that the treatment-naïve cohort (N=4) of Study 304 and the M07-005 study population (all treatment-naïve, N=7) were broadly similar in terms of baseline characteristics. Patients enrolled in both studies had comparable mean (standard deviation (SD)) baseline LDH levels (Study 304 eculizumab treatment-naïve cohort: 961.38 (874.3) U/L; M07-005: 1019.6 (967.3) U/L).

6.13 The proposed PBS initiation criteria for ravulizumab stipulate patients must have a PNH granulocyte clone size ≥ 10%. Although the eligibility criteria for Study 304 required that patients must have a PNH granulocyte clone size ≥ 5%, all patients enrolled in Study 304 had a PNH granulocyte clone size ≥ 10% at baseline, and so did the patients in Study M07-005. Mean (SD) plasma-free haemoglobin was similar between the two studies (Study 304: 23.8 [15.9] mg/dL; M07-005: 17.7 [19.1] mg/dL).

6.14 The submission noted the following differences between the ravulizumab and eculizumab studies in the treatment-naïve population:

- Study 304 enrolled Caucasian patients only, whereas 71.4% of patients in M07-005 were Caucasian. There were more female patients in the M07-005 study compared to Study 304 (57% vs 25%, respectively).
- The proportion of patients with prior packed red blood cells (pRBC) per whole blood transfusions was lower in Study 304 compared with Study M07-005 (50.0% vs 85.7%, respectively).
- PNH-associated conditions prior to informed consent were reported for all patients in Study 304. Three (75.0%) patients had aplastic anaemia, two (50.0%) patients each had anaemia and haematuria or haemoglobinuria. In study M07-

005, three (42.9%) patients had aplastic anaemia, and one patient (14.3%) had haematuria or haemoglobinuria.

6.15 The key features of the included studies are summarised in Table 4.

Table 4: Key features of the included evidence – descriptive indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s) (non-exhaustive)	Use in cost-minimisation analysis
Ravulizumab (proposed medicine for paediatric PNH population)						
Study 304	12	Single arm 26 weeks	High	Complement inhibitor naïve: n=4 Eculizumab experienced: n=8	Change from baseline in LDH, plasma-free haemoglobin, QoL, transfusion avoidance, safety	Not used, Patient weights and TGA approved PI dosing used
Eculizumab (nominated comparator for paediatric PNH population)						
Study M07-005	7	Single arm 12 weeks	High	Complement inhibitor naïve: n=7	Change from baseline in LDH, plasma-free haemoglobin, QoL, PNH clone size, safety	Not used, Patient weights from Study 304 and TGA approved PI dosing used

Source: Sections 2.2-2.5, pp32-42 of the submission.
BTH=breakthrough haemolysis; LDH=lactate dehydrogenase; PD=pharmacodynamic; PNH=Paroxysmal Nocturnal Hemoglobinuria; PK=pharmacokinetic; QoL=quality of life.

6.16 The risk of bias was considered high given the single arm nature of the studies involved in the indirect comparison and the small sample size of the datasets. Awareness of treatment allocation may have affected the reporting of subjective patient outcomes (e.g. safety, quality of life (QoL)). However, these limitations are unavoidable and cannot be adequately addressed given the rarity of PNH in the paediatric population.

Comparative effectiveness

6.17 The assessment of efficacy was a secondary objective in Studies 304 and M07-005 (primary objectives were to assess PK/PD parameters and safety). A summary of PK/PD data is presented in the submission and is not reproduced in this PSD.

6.18 The key efficacy results are summarised in Table 5.

Table 5: Study 304 – Summary of efficacy results in paediatric patients with PNH through primary evaluation Period (FAS)

Key efficacy endpoints	Complement inhibitor treatment naïve patients (n=4)	Eculizumab treatment experienced patients (n=8)
LDH % change from baseline to end of primary evaluation period[a], mean (SD)	-42.09 (58.99)	4.65 (44.70)
Transfusion avoidance[b], n (%)	2 (50.00)	8 (100.00)
FACIT-Fatigue, change from baseline to end of primary evaluation period[a], Mean (SD)	3.00 (6.98)	1.28 (5.24)
Achieved stabilised haemoglobin[c], n (%)	2 (50.00)	6 (75.00)

Source: Table 11, p32 of the Delegate's Overview for ravulizumab; PM- 2021-01659-1-6

FACIT=Paediatric Functional Assessment of chronic illness Therapy; FAS=full analysis set; LDH=lactate dehydrogenase; PNH=Paroxysmal Nocturnal Hemoglobinuria; SD=standard deviation

[a] End of primary evaluation period was defined as Day 183 (Week 26) for Study 304.

[b] Transfusion avoidance was defined as patients who remained transfusion free and did not require a transfusion through Day 183 (Week 26). Percentages were based on the total number of patients in each cohort.

[c] Stabilised haemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26). Percentages were based on the total number of patients in each cohort.

Complement inhibitor treatment-naïve cohort

6.19 The mean (SD) percent change from baseline in LDH on Day 183 was -42.09% (59.00). On Day 183, two patients had a LDH ≤ 1 × ULN and one patient had a LDH ≤ 1.5 × ULN. The fourth patient had a LDH value of 637 U/L on Day 183. The submission noted that this may be attributable to table-top haemolysis (TTH) of the sample suggestive of a likely false event detection.

6.20 Two of four patients (50.0%) remained transfusion free, and two patients (50%) achieved haemoglobin stabilisation[1]. One patient received three blood transfusions administered during treatment for multiple serious adverse events (SAEs) including device-related thrombosis and septic shock. There were no events of breakthrough haemolysis (BTH)[2] during the primary evaluation period (baseline to Day 183).

6.21 No meaningful trends in change of free haemoglobin were observed. Decreases from baseline in mean free haemoglobin levels were observed at Days 15, 43, 71, 99, 127, and 155, but on Day 183, mean free haemoglobin increased to 30.23 mg/dL (108.74% change from baseline) due to values above 450 mg/dL for two patients.

6.22 QoL was assessed using the Paediatric Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire. A mean improvement in FACIT-Fatigue score of ≥ 3 units was considered a clinically meaningful change[3]. This was observed in two patients (50%) at Day 15 which was sustained through to Day 183. On Day 183, the mean (SD) improvement in FACIT-Fatigue score compared to baseline was 3.00 (6.98).

[1] Avoidance of a 2 g/dL (or greater) decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Primary Evaluation Period)

[2] BTH was defined as at least one new or worsening symptom or sign of intravascular haemolysis.

[3] Webster K *et al*. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes*. 2003*;* 1:79

The European Medicines Agency (EMA)[4] has adopted a slightly more conservative level of ≥ 4 points.

Eculizumab treatment-experienced cohort

6.23 During the 26-week primary evaluation period, mean percent change from baseline in LDH remained stable, with mean percent change from baseline ranging between -7.27% and +11.5%.

6.24 All eight (100%) eculizumab-experienced patients remained transfusion free, and six of eight (75%) patients achieved haemoglobin stabilisation. Mean free haemoglobin levels were generally stable over time. None of the patients experienced BTH.

6.25 The eculizumab-experienced cohort had a mean (SD) improvement in paediatric FACIT-Fatigue score of 1.28 (5.24). The submission stated that this improvement was suggestive of stable QoL for patients switching from eculizumab to ravulizumab.

Indirect comparison

6.26 Results for efficacy endpoints commonly reported across Studies 304 and M07-005 in complement inhibitor treatment-naïve patients are summarised in Table 6.

[4] European Medicines Agency. Soliris (eculizumab). 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/soliris

Table 6: Change from baseline in LDH and free haemoglobin between ravulizumab and eculizumab in complement inhibitor treatment-naïve patients across the studies

Endpoints		Ravulizumab Study 304 Complement inhibitor treatment-naïve cohort (N=4)	Eculizumab M07-005 Complement inhibitor treatment-naïve cohort (N=7)
LDH (U/L)			
Baseline	Mean (SD)	961.38 (874.30)	1019.6 (967.34)
	Median (range)	565.90 (444.00, 2269.70)	651.0 (308.00, 3144.00)
End of study (Study 304: 26 weeks; M07-005: 12 weeks)	Mean (SD)	321.00 (212.68)	248.4 (72.36)
	Median (range)	226.00 (195, 64)	217.0 (161, 38)
Change from Baseline	Mean (SD)	-640.38 (988.69)	-771.1 (914.19)
	Median (range)	-339.90 (-2074.70, 193.00)	-467.00 (-2768.00, -103.00)
Percentage change from Baseline, %	Mean (SD)	-42.09 (58.99)	-64.70 (19.29)
	Median (range)	-60.22 (-91.40, 43.50)	-66.70 (-88.00, -33.40)
Free haemoglobin (mg/dL)			
Baseline	Mean (SD)	23.75 (15.92)	17.70 (19.09)
	Median (range)	21.20 (7.60, 45.00)	12.70 (5.30, 60.00)
End of study (Study 304: 26 weeks; M07-005: 12 weeks)	Mean (SD)	30.23 (17.46)	7.44 (3.15)
	Median (range)	32.50 (10.90, 45.00)	8.40 (2.90, 10.90)
Change from Baseline	Mean (SD)	6.48 (20.80)	-10.26 (21.13)
	Median (range)	-2.70 (-6.10, 37.40)	-5.40 (-56.70, 3.90)
Percentage change from Baseline, %	Mean (SD)	108.74 (256.00)	-19.94 (58.79)
	Median (range)	-10.63 (-35.90, 492.10)	-35.50 (-94.50, 55.70)

Source: Table 2.4, p41 of the submission.
LDH=lactate dehydrogenase; SD=standard deviation; U/L=upper limit of normal

6.27 There is very limited precision in the results given the small patient numbers. The median (range) percent reduction from baseline in LDH appeared similar between Study 304 (-60.2% [-91.4, 43.5]) and Study M07-005 (-66.7% [-88.0, -33.4]). However, the mean percent reduction was approximately 23% smaller in Study 304 compared to Study M07-005 (-42.1% *vs.* -64.7%). The submission noted that this may be due to one of the patients in Study 304 having an LDH value of 637 U/L on Day 183, which was likely attributable to a false event.

6.28 The median (range) percent reduction from baseline in free haemoglobin was 25% greater in patients receiving eculizumab in Study M07-005 (-35.5% [-94.5, 55.7]) compared to patients receiving ravulizumab in Study 304 (-10.6% [-35.9, 492.1]). As stated previously, decreases from baseline in mean free haemoglobin levels were observed at Days 15, 43, 71, 99, 127, and 155 in Study 304. However, on Day 183, mean free haemoglobin increased to 30.23 mg/dL (108.74% change from baseline) due to values above 450 mg/dL for two patients. Patients receiving eculizumab in Study M07-005 experienced a mean percent reduction of 19.94%.

Comparative harms

6.29 A comparison of overall safety outcomes reported by patients receiving ravulizumab in Study 304 and patients receiving eculizumab in Study M07-005 is presented in Table 7.

Table 7: Summary of key adverse events in Studies 304 and M07-005

	Ravulizumab (Study 304)		Eculizumab (Study M07-005)
	Eculizumab treatment-naïve cohort (N=4)	Eculizumab treatment-experienced cohort (N=8)	Eculizumab treatment-naïve (N=7)
Duration of therapy (days) Mean (SD) Median (range)	 183.3 (0.50) 184.0 (183, 184)	 183.3 (0.89) 183.0 (182, 185)	 85.3 (2.06) 85.0 (82.0, 89.0)
Any AE, n/N (%)	3/4 (75.0%)	7/8 (87.5%)	7/7 (100.0%)
Any SAE, n/N (%)	1/4 (25.0%)	2/8 (25.0%)	2/7 (28.6%)
AEs possibly or probably related to study drug, n/N (%)[a]	1/4 (25.0%)	3/8 (37.5%)	5/7 (71.4%)
SAEs possibly or probably related to study drug, n/N (%)[a]	0/4 (0.0%)	0/8 (0.0%)	1/7 (14.3%)

Source: Modified from Table 2.6, p43 of the submission.
AE=adverse event; SAE=serious adverse event; SD=standard deviation
[a] Related AEs were defined as AEs that were possibly, probably, or definitely related to study treatment.
Note: Data have not been included for AEs or SAEs leading to discontinuation of study drug, AEs of special interest (meningococcal infection), and deaths, as these events were not observed in either of the studies.

6.30 Among complement inhibitor treatment-naïve patients, three of four patients (75%) in Study 304 and all seven patients (100%) in Study M07-005 experienced at least one treatment emergent adverse event (TEAE) related to any cause. Similar proportions of patients experienced a SAE related to any cause (Study 304: 25% in Study 304 vs 29% in Study M07-005).

6.31 TEAEs which were considered possibly or probably study drug-related occurred in 25% and 38% of patients in the treatment-naïve and eculizumab-experienced cohorts, respectively, in Study 304, and in 71% of patients (all treatment-naïve) in Study M07-005.

6.32 Among complement inhibitor treatment-naïve patients in Study 304, each of the following TEAEs (non-exhaustive) was reported in one patient (1/4; 25%): Cushing's syndrome, device-related thrombosis, multiple organ dysfunction syndrome, pyrexia, nasopharyngitis, device-related sepsis, septic shock, staphylococcal infection, increased blood pressure and arthralgia.

6.33 The most frequently reported adverse events (AEs) in Study M07-005 were abdominal pain, pyrexia, upper respiratory tract infection, contusion and cough, each reported in two patients (28.6%).

6.34 The frequencies of TEAEs and SAEs in the paediatric PNH population treated with ravulizumab in Study 304 appeared consistent with those reported for the adult PNH population in the ravulizumab arms of Studies 301 and 302:

- The safety data from Studies 301 and 302 suggest that ravulizumab has a similar safety profile to eculizumab in adult patients with PNH.
- The frequency of any AE was approximately 88% in Studies 301 and 302, compared with 75% and 88% in the treatment-naïve and eculizumab-experienced cohorts, respectively, in Study 304.
- The frequency of AEs related/possibly related to study drug was 25% and 41% in the ravulizumab arms of Studies 302 and 031, respectively, compared with 25% and 38% in the treatment-naïve and eculizumab-experienced cohorts, respectively, in Study 304.
- All patients in the ravulizumab studies received a meningococcal vaccine before commencing treatment and no meningococcal infections were reported in any of the studies.

6.35 Due to the small number of patients and the single arm design of the included paediatric studies, the assessment of comparative safety is unreliable and difficult. The results need to be interpreted in the context of the rarity of the condition. Notwithstanding these limitations, the totality of the evidence for safety suggests that ravulizumab likely has a similar safety profile to that of eculizumab in the paediatric population with PNH.

6.36 The extended safety assessment of ravulizumab in the submission was based on the Australian Specific Annex (ASA) to the EU Risk Management Plan (RMP) Version 4.0 (dated 31 October 2022) and the latest Periodic Benefit-Risk Evaluation Report (PBRER) for the reporting interval from 1 July 2021 through 31 December 2021. The identified and potential risks associated with ravulizumab (such as infections caused by Neisseria meningitidis) are consistent with those associated with eculizumab. It is expected that risk minimisation measures such as meningococcal vaccination would mitigate this risk.

Benefits/harms

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

Clinical claim

6.38 The submission described ravulizumab as non-inferior in terms of effectiveness and safety compared to eculizumab in paediatric patients with PNH.

6.39 The key limitations with the evidence were the very small number of patients in the studies (12 patients and 7 patients in the ravulizumab and eculizumab studies, respectively) and the single arm nature of the studies involved in the indirect comparison. A rigorous assessment of transitivity and statistical analyses for hypothesis testing were not feasible. However, the estimated worldwide incidence of PNH is rare (1.3 per million population) and paediatric cases account for only 5-10% of reported cases of PNH (TGA Delegate's Overview for ravulizumab, PM-2021-01659-

1-6). Therefore, any forthcoming evidence is likely to have similar limitations. Ravulizumab is also a pharmacological analogue of eculizumab. Taken together, the data suggest that ravulizumab is likely to be non-inferior in terms of effectiveness and safety to eculizumab in paediatric patients with PNH.

6.40 The PBAC considered that the claim of non-inferior comparative effectiveness and safety, while based on very limited data, was overall likely to be reasonable.

Economic analysis

6.41 The submission presented a CMA of ravulizumab compared to eculizumab for the treatment of paediatric PNH patients. Of note, the proposed effective price in the submission was the same as the current effective price of ravulizumab (for adults) and was lower than the cost-minimised price for paediatric patients from the CMA. The key components and assumptions are shown in Table 8.

Table 8: Key components of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2 of the submission, effectiveness is assumed to be non-inferior. This was reasonable.
Therapeutic claim: safety	Based on evidence presented in Section 2 of the submission, safety is assumed to be non-inferior. This was reasonable.
Evidence base	Unanchored indirect comparison of the key single arm ravulizumab study (Study 304) and a single arm eculizumab study (Study M07-005).
Duration of treatment costed	2 years. This was reasonable and consistent with previous PBAC advice (para 7.15, ravulizumab, PSD, July 2021 PBAC meeting).
Population	All complement inhibitor treatment naïve (i.e. loading doses are included for both ravulizumab and eculizumab). This was not consistent with the proposed PBS listing which allows eculizumab-experienced patients to switch to ravulizumab nor with the financial analysis (which estimated ravulizumab use only in patients who switch). However, this was consistent with the CMA approach accepted by the PBAC when it considered the listing of ravulizumab for the adult PNH population, which included a loading dose for eculizumab (para 7.15, ravulizumab PSD, July 2021 PBAC meeting)[a].
Equi-effective dose	Ravulizumab 41,875mg (13.75 administrations including a loading dose) is equal to eculizumab 47,350mg (53.84 administrations including loading doses).[b] (based on the distribution of body weight from Study 304 and dose regimens recommended in the PI documents)
Direct medicine costs	At proposed effective prices, ravulizumab is estimated to have a lower cost than eculizumab over the first two years of treatment, as the proposed AEMP is lower than the price per vial derived from the CMA. The distribution of patient body weight which affected the dose received, was based on the ravulizumab study (Study 304). While this source was reasonable, given the small sample size (n = 12), the weight distribution applied may not be reliable.
Cost offsets	IV administration per dose ($46.15, MBS Item 105). This was reasonable and consistent with previous PBAC advice (para 7.15, ravulizumab, PSD, July 2021 PBAC meeting).

Source: Constructed during the evaluation from the "Section 3 CMA workbook" attachment provided with the submission.
AEMP = approved ex-manufacturer price; CMA = cost-minimisation analysis; IV = intravenous; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; PNH = paroxysmal nocturnal haemoglobinuria; PSD = public summary document.
[a] Eculizumab loading dose of 4 × 600mg and maintenance dose of 50 × 900mg over two years (total dose = 47,400mg)
[b] Doses and number of administrations weighted for patients at different weight categories (17% ≥30−<40 kg, 33% ≥40−<60 kg, and 50% ≥60−<100 kg).

6.42 The proposed equi-effective doses over the first two years of treatment were:

- Ravulizumab 41,875 mg (based on a weighted loading dose of 2,350 mg and 12.75 × 3,100 mg maintenance doses) is equivalent to eculizumab 47,350 mg (based on weighted 3.67 × 600 mg loading doses and 50.17 × 900 mg maintenance doses).

This was based on the dosing schedule detailed in Table 1

6.43 The derivation of costs over the first two years of treatment was reasonable and consistent with previous PBAC advice when ravulizumab was considered for the adult PNH population (para 7.15, ravulizumab, PSD, July 2021 PBAC meeting).

6.44 This approach, however, assumed all patients were complement inhibitor treatment-naïve (i.e. loading doses of both ravulizumab and eculizumab were included). This may not be reasonable, as the proposed PBS listing allowed treatment switching from eculizumab to ravulizumab and patients already on eculizumab therapy did not require eculizumab loading doses. In addition, the assumption of 100% treatment-naïve patients in CMA was not consistent with the approach assumed in the financial analysis, which assumed all patients would switch. However, the calculated cost-minimised price per vial for ravulizumab by assuming only maintenance dosing of eculizumab was higher than effective prices proposed in the submission (see Table 10).

6.45 Doses applied were consistent with the approved PIs of ravulizumab and eculizumab for the paediatric population. As dosing is weight-based, the distribution of weights applied was based on the key ravulizumab trial (Study 304). While this source was reasonable, the submission erroneously swapped the proportions of patients in the ≥ 40−< 60 kg and ≥ 60−< 100 kg categories (50.0% and 33.3%, respectively, as reported in Table 9 of the Study 304 Clinical Study Report (CSR), compared to 33.3% and 50.0%, respectively, used in the CMA). The resulting cost-minimisation price increased when the correct weight distribution was applied in sensitivity analyses (Table 10). Nonetheless, given the small number of patients enrolled in Study 305 (n = 12), the weight distribution applied is associated with considerable uncertainty. However, as the proposed price was based on the effective price (and therefore distribution of weight) that was accepted in the adult submission (para 6.66, ravulizumab, PSD, July 2021 PBAC meeting)., ravulizumab is not likely to be associated with additional costs over eculizumab.

6.46 The submission included a cost-offset based on a reduction in IV administration costs due to the lower dose frequency of ravulizumab. Administrations were costed as a subsequent specialist attendance appointment ($46.15, MBS item 105). This was reasonable and consistent with previous PBAC advice (para 7.15, ravulizumab, PSD, March 2021 PBAC meeting). Costs attributed to AEs were not included in the CMA. This may be reasonable as the submission claimed non-inferior safety to eculizumab.

6.47 The results of the CMA, based on current effective price of eculizumab, is summarised in Table 9. The resulting cost-minimisation price was higher than the effective price for ravulizumab proposed in the submission.

Table 9: Results of the cost-minimisation approach for ravulizumab

Description	Cost
Total dose of eculizumab over two years	47,350 mg[a]
Number of 300 mg eculizumab vials	157.83
Effective AEMP per 300 mg vial of eculizumab	$
Cost of eculizumab acquisition	$
Number of eculizumab administrations	53.83
Cost of eculizumab administrations ($46.15, MBS item 105)	$2,484.41
Total eculizumab cost per patient	$
Number of ravulizumab administrations	13.75
Cost of ravulizumab administrations ($46.15, MBS item 105)	$634.56
Price of ravulizumab acquisition to match	$
Total dose of ravulizumab over two years	41,875 mg[b]
Price per mg of ravulizumab	$ per mg[c]
Cost-minimisation price per vial of ravulizumab	300 mg vial: $[c] 1,100 mg vial: $[c]
Proposed AEMP of ravulizumab per vial (the same as the effective AEMP for adult population)	300 mg vial: $ 1,100 mg vial: $

Source: Constructed during the evaluation from the "Section 3 CMA workbook" provided with the submission.
AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule
[a] Over two years, 3.67 × 600 mg loading doses (17% × 2 600 mg doses, 83% × 4 600 mg doses) and 50.17 × 900 mg maintenance doses (17% × 51 900 mg doses, 83% × 50 900 mg doses) (total dose 47,350 mg, over 53.83 doses), where 17% of patients were assumed to weigh ≥ 30−< 40 kg and 83% ≥ 40 kg.
[b] Over two years, patients were assumed to receive an average loading dose of 2,350 mg (17% × 1,200 mg, 33% × 2,400 mg, 50% × 2,700 mg) and 12.75 × 3,100 mg maintenance doses (17% × 2,700 mg, 33% × 3,000 mg, 50% × 3,300 mg) (total dose 41,875 mg, over 13.75 doses), where 17% of patients were assumed to weigh ≥ 30−< 40 kg; 33% ≥ 40−< 60 kg and 50% ≥ 60 kg.
[c] Reported in the submission as $. However, costs were revised during the evaluation as the submission had divided the total cost of eculizumab treatment by the total dose of ravulizumab without first subtracting ravulizumab administration costs.

6.48 The submission did not present any sensitivity analyses to test alternate estimates or assumptions. Sensitivity analyses were performed during the evaluation by: i) assuming no loading doses for eculizumab patients and ii) altering the weight distribution of patients. These are presented in Table 10.

Table 10: Key sensitivity analyses on the cost-minimisation

Analyses	Results	% change from revised base case	Absolute price difference compared with AEMP (proposed AEMP - resulting cost minimisation price)
Revised base case[a]	**300 mg vial: $[redacted] 1,100 mg vial: $[redacted]**	**0%**	**-$[redacted] -$[redacted]**
Proposed AEMP	300 mg vial: $[redacted] 1,100 mg vial: $[redacted]	-6.05%	$[redacted] $[redacted]
Eculizumab loading dose (base case: included) Exclude[b]	300 mg vial: $[redacted] 1,100 mg vial: $[redacted]	-1.17%	-$[redacted] -$[redacted]
Weight distribution of patients (base case with erroneous proportions (see para 6.42): 17% ≥ 30−< 40 kg; 33% ≥ 40−< 60 kg and 50% ≥ 60−<100 kg)			
Corrected distribution, as per Study 304[c]	300 mg vial: $[redacted] 1,100 mg vial: $[redacted]	1.67%	-$[redacted] -$[redacted]
All patients weigh ≥ 30 to < 40 kg	300 mg vial: $[redacted] 1,100 mg vial: $[redacted]	16.92%	-$[redacted] -$[redacted]
All patients weigh ≥ 40 to < 60 kg	300 mg vial: $[redacted] 1,100 mg vial: $[redacted]	3.12%	-$[redacted] -$[redacted]
All patients weigh ≥ 60 to < 100 kg	300 mg vial: $[redacted] 1,100 mg vial: $[redacted]	-6.38%	+$[redacted] +$[redacted]

Source: Constructed during the evaluation from the "Section 3 CMA workbook" attachment and Table 9 pg. 49 of the "Attach 4 304-report body" attachment provided with the submission.
AEMP = approved ex-manufacturer price; CSR = clinical study report.
[a] The base case was revised during the evaluation as the submission had divided the total cost of eculizumab treatment by the total dose of ravulizumab without first subtracting ravulizumab administration costs.
[b] This would be observed in a setting where all patients are receiving eculizumab maintenance doses and 100% of these patients will switch from eculizumab (no loading doses needed) to ravulizumab (loading dose needed).
[b] 17% ≥30−<40 kg; 50% ≥40−<60 kg and 33% ≥60−<100 kg.

6.49 The proposed approved ex-manufacturer price (AEMP) for ravulizumab is [redacted]% lower than the resulting price from the base case CMA. The cost-minimised prices from the majority of sensitivity analyses performed during the evaluation remained higher than the proposed AEMP. The exception to this was an analysis exploring the assumption that all patients would weigh ≥ 60 to < 100 kg. However, as the proposed price was derived from a CMA based on the distribution of body weight that was accepted in adults (which included patients weighing < 60 kg)[5], ravulizumab is not likely to be associated with additional costs over eculizumab. The Pre-PBAC Response argued that given the request is for the paediatric population, it would be inappropriate to rely on an analysis which excludes patients weighing less than 60 kg.

6.50 As mentioned previously (paragraph 6.42), the submission had included eculizumab loading doses in the CMA which was not consistent with the financial analysis.

[5] As the average ravulizumab dose in adults reported in the PSD (44,616 mg) was lower than the total dose in patients weighing ≥60 kg (**Error! Reference source not found.Error! Reference source not found.**), some use in patients weighing <60 kg was included.

However, excluding these doses from the CMA did not reduce the resulting cost-minimised price to below the proposed AEMP.

Drug cost/patient/year

6.51 Drug costs per patient per year are presented in Table 11. At the proposed effective AEMP of $ per 300 mg vial, the estimated drug cost for ravulizumab per patient was $ (72.42 vials for loading and maintenance doses) in the initial year and $ per subsequent year (67.17 vials for maintenance doses only).[6]

Table 11: Drug cost per average patient per year

	Ravulizumab			Eculizumab		
	Study 304 (183 days)	**Cost Minimisation**	**Financials**	**Study M07-005** (86 days)	**Cost Minimisation**	**Financials**
Total dose per year (revised)	11,500mg[a]	Yr 1: 21,725mg[b] Yr 2: 20,150mg[c]	Yr 1: 21,100mg[d] (21,725mg)[b] Yr 2: 20,150mg[c]	6,875mg[e]	Yr 1: 23,953mg[f] Yr 2: 23,400mg[g]	23,400mg[h]
Total cost per year (revised)	$[i]	Yr 1: $[j] Yr 2: $[j]	Yr 1: $[k] ($[k]) Yr 2+: $[k]	$[l]	Yr 1: $[m] Yr 2: $[m]	$[n]

Source: Constructed during the evaluation from the "Attach 4 304-report body", "Section 3 CMA workbook" and the "Section 4 BIM workbook" provided with the submission.

Yr = year.

Note: Drug doses, and costs were calculated for the average patient where 17% of patients were assumed to weigh ≥30−<40 kg; 33% ≥40−<60 kg and 50% ≥60 kg. The 1,100mg vials were not considered as they have the same cost (per mg) as the 300 mg vial.

Financial estimates were revised during the evaluation as the submission had erroneously estimated the number and dose of ravulizumab scripts in year 1.

[a] Mean cumulative dose of 11,500 mg per ravulizumab patient over 183 days (the duration of the trial).

[b] 1 × 2,350 mg (7.83 vials) loading dose + 6.25 × 3,100 mg (10.33 vials) maintenance doses.

[c] 6.50 × 3,100 mg (10.33 vials).

[d] 1 × 2,350 mg (7.83 vials) loading dose + 12.50 × 1,500 mg (5.00 vials) maintenance doses. In the financial analysis, the frequency of administration and dose per administration for maintenance doses in Year 1 were not consistent with the cost-minimisation analysis. This has been revised during the evaluation.

[e] Mean cumulative dose of 6,857 mg per eculizumab patient over 86 days (the duration of the trial).

[f] 1 × 2,200 mg (7.33 vials) loading dose + 24.17 × 900 mg (3.00 vials) maintenance doses.

[g] 26.00 × 900 mg (3.00 vials).

[h] 13.00 × 1,800 mg (6.00 vials) (each script is sufficient for 2 administrations as per the maximum quantity).

[i] 11,500 mg / 300 mg vial × $ (effective AEMP per vial)

[j] Number of vials × $ (effective AEMP per vial)

[k] Number of vials × $ (dispensed price per vial, weighted for 92% public hospital use (no additional fees) and 8% private hospital use ($40 remuneration fee and $7.78 ready prepared fee).

[l] 6,875 mg / 300 mg vial × $ (effective AEMP per vial)

[m] Number of vials × $ (effective AEMP per vial)

[n] Number of vials × $ (dispensed price per vial, weighted for 92% public hospital use (no additional fees) and 8% private hospital use ($40 remuneration fee and $7.78 ready prepared fee).

6.52 The inclusion/exclusion of loading doses for eculizumab was inconsistent between the CMA and financial analysis, where all patients in the CMA were assumed to be complement inhibitor treatment-naïve (and so loading doses for eculizumab were included), compared to the assumption in the financial analysis that all patients would switch from eculizumab (no loading doses for eculizumab included).

[6] The number of vials was determined based on the average dose where 17% of patients were assumed to weigh ≥30−<40 kg; 33% ≥40−<60 kg and 50% ≥60 kg.

Estimated PBS usage & financial implications

6.53 This submission was not considered by DUSC. The submission presented a market share approach to estimate the use and financial implications for listing ravulizumab on the PBS based on the current use of eculizumab in paediatric patients.

6.54 Key parameters and sources used in the financial estimates are presented in Table 12.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible population		
Incidence and prevalence of paediatric PHN population.	Incidence: 0% Prevalence: [redacted] patients. Based on commissioned DUSC report.	The assumption of no incident patients over the next 6 years is uncertain, however the PBAC agreed this may be reasonable, given the rarity of this condition in the paediatric population.
Treatment utilisation		
Uptake rate	100%	Reasonable.
Average number of ravulizumab scripts per patient per year	Loading dose: 1 script Maintenance dose in year 1: 12.50 (revised: 6.25[a]) scripts Maintenance dose in year 2+: 6.50 scripts[a]	This was reasonable; however, the submission had erroneously double counted the number of scripts in year 1.
Dose per ravulizumab script	Loading dose: 2,350 mg Year 1 maintenance dose: 1,500 mg Year 2 maintenance dose: 3,100 mg Based on the weighted doses derived from the CMA.	The year 1 maintenance dose differed from year 2, this was not justified and appears to be erroneous.
Cost per ravulizumab script	Loading dose script: $[redacted] (7.83 × 300 mg vials) Year 1 Maintenance dose script: $[redacted] (5.00 × 300 mg vials) Year 2 Maintenance dose script: $[redacted] (10.33 × 300 mg vials) The proposed effective AEMP price per 300 mg vial ($[redacted])[b] was used and the number of 300 mg vials required per script was derived from the CMA. The cost per script was then weighted for 92.27% public hospital use (no additional fees) and 7.73% private hospital use ($40.00 HSD pharmacy mark up and $7.78 ready prepared fee), based on 2021 eculizumab usage in the paediatric and adult population.	As stated above the dose per year 1 maintenance script does not appear to be accurate however this approach was reasonable, noting that the dispensing fee applied of ($7.78) was not current ($7.82).
Average number of eculizumab scripts per patient per year	Maintenance dose: 13 scripts (equating to one script every 4 weeks). Assuming each script would be sufficient to cover 2 administrations as the maximum quantity allows for 6 × 300 mg vials (3 vials per administration).	Reasonable.
Dose per eculizumab script	1,800 mg (costed as 6 × 300 mg vials per script), which covers 2 administrations of 900 mg, in line with the weighted dose derived from the CMA.	Reasonable.
Cost per eculizumab script	Maintenance dose: $[redacted]. 6 × $[redacted] (effective AEMP for 300 mg vial). Weighted for public and private hospital use as noted for ravulizumab.	Reasonable.

Parameter	Value applied and source	Comment
Patient copayment	PBS: $25.15, weighted by eculizumab PBS utilisation data by beneficiary ($42.50 for general and $6.80 for concession). No RPBS patients were identified from 2021 eculizumab PBS utilisation data.	The updated fees for general and concession PBS patients are $30.00 and $7.30. This does not substantially impact the financial estimates. It may be prudent to confirm no RPBS patients were present in 2022.
MBS items	MBS item 105 (subsequent specialist consultation) was costed (100% benefit) for each script.	This source was reasonable however the submission did not multiply the number of services by the number of ravulizumab patients and has used the 100% benefit instead of the 80% benefit as suggested in the PBAC guidelines. The PSCR accepted the correction of the MBS costs.

Source: Constructed during the evaluation from the "Section 4 BIM workbook" provided with the submission.
AEMP = approved ex-manufacturer price; CMA = cost-minimisation analysis; DUSC = Drug Utilisation Sub-Committee; HSD = highly specialised drugs; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PHN = paroxysmal nocturnal hemoglobinuria; PI = Product Information; RPBS = Repatriation Pharmaceutical Benefits Scheme, PSCR = Pre-Sub-Committee Response.
[a] One script every 8 weeks, 2 weeks after loading dose.
[b] The 1,100 mg vials were not considered in the financial analyses as they have the same cost (per mg) as the 300 mg vial.
The redacted values correspond to the following range:
[1] < 500

6.55 A DUSC report commissioned by the sponsor, identified a total of < 500 patients under 18 years old who are currently treated with eculizumab for PNH. The submission considered both of these patients would switch over to ravulizumab and hence only ravulizumab loading does were included in the financial estimates. This was reasonable. The submission also assumed there would be no new paediatric cases of PNH over the next 6 years. This is uncertain but may be reasonable given the rarity of this condition in the paediatric population.

6.56 The submission double counted the number of ravulizumab maintenance scripts in the first year of treatment, assuming 12.5 scripts per patient, equivalent to a script every 4 weeks. The PI indicates an administration every 8 weeks for patients who weigh above 20 kg. The submission also assumed that each ravulizumab maintenance script in Year 1 would incur the cost of 5 × 300 mg vials. This is not consistent with the number of vials costed in Year 2+ which was derived from the CMA (10.3 × 300 mg vials equating to a dose of 3,100 mg). The number of ravulizumab scripts in Year 1 was revised during the evaluation to a maintenance script every 8 weeks (starting 2 weeks after the loading dose), equating to 6.25 maintenance scripts in Year 1. The cost of ravulizumab maintenance scripts in Year 1 was revised to equal to the cost of maintenance scripts in Year 2+ ($).

6.57 The Pre-Sub-Committee Response (PSCR) accepted the revisions undertaken during the evaluation relating to adjusting for double counting scripts in year 1 and corrected MBS benefit level (80% instead of 100%) (see Table 13). The updated financial estimates are presented in Table 13. The revised results indicate reduced cost-savings to the PBS/RPBS in the first year (net cost saving vs net cost saving as estimated in the submission).

Table 13: Estimated use and financial implications *(PSCR updated)*

	2023	2024	2025	2026	2027	2028
Patients switching from eculizumab to ravulizumab (100% of patients)[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Yr 2+ ravulizumab patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of ravulizumab loading dose scripts (1 per patient)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost of ravulizumab loading dose scripts ($[redacted] per script)[b,c]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of maintenance dose scripts yr 1 patients (12.5 per patient)[d] (revised 6.25 per patient)[e]	[redacted][1] ([redacted][1])	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of maintenance dose scripts for yr 2+ patients (6.5 per patient)[e]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost of maintenance dose scripts. ($[redacted][c,f] per year 1 script, $[redacted] per year 2 script)[c,g] (Revised to $[redacted] in both years)[c,g]	[redacted][2] ([redacted][2])	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total cost of ravulizumab to the PBS, less copays[h]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Substituted eculizumab scripts (13 scripts per patient)[i]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Reduction to the PBS for substituted eculizumab scripts ($[redacted] per script), less copays[c,h,j]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to PBS/RPBS (revised)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to MBS[k] (revised)[l]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to PBS/RPBS/MBS (revised)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]

Source: Constructed during the evaluation from the "Section 4 BIM workbook" attachment provided with the submission.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Yr = year.

[a] DUSC report commissioned by the sponsor indicates that there are currently two paediatric patients treated with eculizumab in Australia.
[b] Cost per script based on average loading dose of 2,350 mg (derived in the cost minimisation analysis), equivalent to 7.83 × 300 mg vials at an AEMP of $[redacted] per vial.
[c] Weighted for 92% public hospital use (no additional fees) and 8% private hospital use ($40 HSD pharmacy mark-up and $7.78 ready prepared fee).
[d] The submission had erroneously estimated 12.5 Year 1 ravulizumab maintenance scripts per patient.
[e] Ravulizumab script every 8 weeks, starting 2 weeks after the loading dose as per the PI.
[f] Weighted (for public/private use) cost per script based on 5 × 300 mg vials at an AEMP of $[redacted] per vial.
[g] Weighted (for public/private use) cost per script based on average dose of 3,100 mg (derived in the cost minimisation analysis), equivalent to 10.33 × 300 mg vials at an AEMP of $[redacted] per vial.
[h] Patient copayment of $25.15 per script, weighted by eculizumab PBS utilisation data by beneficiary, (52% $42.50 (general), 45% $6.80 (concession) and 3% $0.00 (concessional free)
[i] One eculizumab script every 4 weeks (as each script is sufficient for 2 administrations).
[j] Weighted (for public/private use) cost per script based on 2 average doses of 900 mg each (derived in the cost-minimisation analysis), equivalent to 6.00 × 300 mg vials at an AEMP of $[redacted] per vial.
[k] 100% benefit of MBS item 105 ($46.15, subsequent specialist visit) for 7.25 and 6.50 administrations in Year 1 and 2+ for ravulizumab and 26 administrations per year for eculizumab. Administrations for one patient only. *The 80% MBS rebate has been applied in the estimates.*
[l] Costs to the MBS were revised during the evaluation as the submission estimated costs for one patient only and had applied the MBS fee of item 105 instead of the 80% benefit ($36.92) which is recommended in the PBAC guidelines.
The redacted values correspond to the following ranges:
[1] < 500
[2] $0 to < $10 million
[3] Net cost saving

Financial Management – Risk Sharing Arrangements

6.58 The submission proposed no changes to the existing RSA established prior to the listing of eculizumab and ravulizumab on 1 March 2022 for the treatment of PNH.

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

7 PBAC Outcome

7.1 The PBAC recommended amending the Section 100 – Highly Specialised Drugs Program (Public and Private Hospital) listings of ravulizumab to permit use in paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH). In making this recommendation, the PBAC was satisfied the available evidence, while limited due to the rarity of PNH in children, supports a conclusion that ravulizumab is likely to be of non-inferior comparative effectiveness and safety to eculizumab in this patient population. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of ravulizumab would be acceptable if it were cost-minimised against eculizumab.

7.2 The Committee considered the equi-effective doses were ravulizumab 41,875 mg (based on a weighted loading dose of 2,350 mg and 12.75 x 3,100 mg maintenance doses) = eculizumab 47,350 mg (based on weighted 3.67 x 600 mg loading doses and 50.17 x 900 mg maintenance doses).

7.3 The PBAC considered that while paediatric patients were eligible for treatment with eculizumab and the clinical need for an additional therapy was modest, it also considered the reduced frequency of the dosing regimen (8 weekly in maintenance therapy for ravulizumab versus fortnightly for eculizumab) would be beneficial for paediatric patients resulting in fewer time-consuming hospital visits and infusions. The PBAC noted there was currently inequitable PBS access for adults and paediatric patients with PNH.

7.4 With respect to the requested listings, the PBAC considered the proposal to remove the age restriction on the listings of ravulizumab for PNH was reasonable, and a unique restriction for the paediatric population was not required. The PBAC noted the extension to the PBS listing to include paediatric patients would resolve current equity issues for these patients by providing an effective treatment option with reduced hospital attendances and infusion frequency, which can be highly impactful on children.

7.5 The PBAC considered the nominated comparator of eculizumab was reasonable as it is currently PBS listed for the treatment of PNH in paediatric patients.

7.6 The PBAC noted the clinical evidence for ravulizumab and eculizumab studies was very limited, with only single arm trials with very few patients (N=12 for the ravulizumab trial and N=7 for the eculizumab trial). The Committee further noted the evaluation concluded a rigorous assessment of transitivity statistical analyses was not possible with the available data resulting in limited precision in the differences in the level of

change in lactate dehydrogenase (LDH) and free haemoglobin levels between eculizumab and ravulizumab in paediatric patients. However, the PBAC noted ravulizumab and eculizumab are pharmacological analogues, and there was no evidence to suggest the effectiveness or safety of ravulizumab compared to eculizumab in paediatric patients would be different to the adult population. Overall, the PBAC considered ravulizumab was likely to be of non-inferior comparative effectiveness to eculizumab for PNH in paediatric patients.

7.7 The Committee noted the evidence for safety and adverse events was limited in the paediatric population due to the small number of patients in the clinical trials; however, also noted the available evidence suggested similar frequency and types of adverse events between ravulizumab and eculizumab, and further noted all patients require meningococcal vaccination and prophylactic penicillin. Overall, the PBAC considered it was reasonable to conclude the available (but limited) data suggest ravulizumab is likely to be of non-inferior comparative safety to eculizumab in paediatric patients with PNH.

7.8 The PBAC considered the methodology of the cost minimisation approach (CMA) used in the submission was reasonable and it accepted the more conservative proposed price of ravulizumab which was the same as that accepted for the adult population. The PBAC considered that while there were some uncertainties in the CMA associated with the distributions of weight (given the small number of patients) and with treatment switching not being accounted for, it noted the additional sensitivity analyses in the evaluation did not result in a lower equi-effective price than was offered and overall the Committee was of the view the approach was acceptable as it would not be associated with additional costs over eculizumab.

7.9 The PBAC considered that the assumption of two prevalent patients, with an incidence of zero additional patients over 6 years was uncertain, however considered that given the relatively well documented incidence of PNH in children, this estimate was likely to be reasonable (although it was possible a case may occur in this period). The PBAC noted the issues with double counting the number of ravulizumab maintenance prescriptions and predicted MBS costs had been revised and accepted by the Sponsor (paragraph 6.57 refers) and considered the revised financial estimates, which estimated a modest save to the PBS, were likely to be reasonable. The PBAC also considered the proposal of no increase to the current financial expenditure caps for PNH provided additional certainty as to the likely overall expenditure on ravulizumab for PNH.

7.10 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ravulizumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over eculizumab, 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.

7.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

MEDICINAL PRODUCT **medicinal product pack**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
RAVULIZUMAB				
Ravulizumab 300 mg/3 mL injection, 3 mL vial	1	1	2	Ultomiris
Ravulizumab 1.1 g/11 mL injection, 11 mL vial	1	1	2	Ultomiris
Proposed PBS restriction: initiation for complement inhibitor-naïve patients with PNH				
Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private)				
Prescriber type: ☒Medical Practitioners				
Restriction type: ☒Authority Required – written				
Episodicity: Not applicable				
Severity: Not applicable				
Condition: Paroxysmal nocturnal haemoglobinuria (PNH)				
Treatment Phase: Initial treatment- Initial 1 (new patient)				
Restriction: Authority Required - written				
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				
Clinical criteria:				
Patient must not have received prior treatment with this drug for this condition, AND				
Patient must have a diagnosis of PNH established by flow cytometry, AND				
Patient must have a PNH granulocyte clone size equal to or greater than 10%, AND				
Patient must have a raised lactate dehydrogenase value at least 1.5 times the upper limit of normal, AND				
Patient must have experienced a thrombotic/embolic event which required anticoagulant therapy; OR				
Patient must have been transfused with at least 4 units of red blood cells in the last 12 months, OR				
Patient must have chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple haemoglobin measurements not exceeding 70 g/L in the absence of anaemia symptoms; OR				
Patient must have chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple red blood cell measurements not exceeding 100 g/L in addition to having anaemia symptoms; OR				
Patient must have debilitating shortness of breath/chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded; OR				
Patient must have a history of renal insufficiency, demonstrated by an eGFR less than or equal to 60 mL/min/1.73m^2, where causes other than PNH have been excluded; OR				
Patients must have recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded, AND				
The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan				
~~**Population criteria**: Patient must be at least 18 years of age.~~				

Prescribing instructions: At the time of the authority application, medical practitioners should request the appropriate number of vials, to provide for a single infusion to cover the loading dose and maintenance doses based on the patient's weight and as per the Product Information. Refer to the Product information for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1100 mg in 11 mL vials).
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. EST 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 No increase in the maximum number of repeats may be authorised
Caution: WARNING: This drug increases the risk of meningococcal infections (sepsis and/or meningitis). Consult the approved PI for information about vaccination against meningococcal infection.

Requested restriction for ravulizumab –for patients transitioning from eculizumab to ravulizumab (abridged)
Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private)
Condition: Paroxysmal nocturnal haemoglobinuria
PBS indication: Paroxysmal nocturnal haemoglobinuria
Restriction type: ☒Authority Required – written
Treatment Phase: Initial treatment- Initial 2 (switching from eculizumab)
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
Clinical criteria:
Patient must have previously received eculizumab for the treatment of this condition funded under the Australian Government's Life Saving Drugs Program (LSDP), OR
Patient must have received prior PBS-subsidised treatment with this drug for this condition; AND
Patient must have a diagnosis of PNH established by flow cytometry prior to LSDP-funded treatment with eculizumab, AND received prior PBS-subsidised treatment with eculizumab through the 'Initial treatment - Initial 2 (switching from PBS-subsidised ravulizumab for pregnancy)' criteria; AND
The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan
~~**Population criteria**: Patient must be at least 18 years of age.~~

Requested restriction for ravulizumab – continuing treatment
Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private)
PBS indication: Paroxysmal nocturnal haemoglobinuria
Restriction type: ☒Authority Required – written
Treatment Phase: continuing treatment
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
Clinical criteria:
First Continuing Criteria: Patient must have received PBS-subsidised treatment with this drug for this condition under the 'Initial' or 'Grandfather' treatment restriction, AND The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan. Subsequent Continuing Treatment: Patient must have previously received PBS-subsidised treatment with this drug for this condition under the 'First Continuing Treatment' or 'Return' criteria, AND 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 The treatment must not be in combination with any of (i) another Complement 5 (C5) inhibitor, (ii) pegcetacoplan.
~~**Population criteria**: Patient must be at least 18 years of age.~~

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.