

7.04 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.**

ECULIZUMAB

**Solution concentrate for I.V. infusion 300 mg in
30 mL,
Soliris[®],
Alexion Pharmaceuticals Australasia Pty Ltd.**

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 100, Authority Required listing for ravulizumab for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH).
- 1.2 The resubmission aimed to address concerns expressed by the PBAC with the July 2020 ravulizumab submission for PNH as well as the PBAC's July 2020 request for a cost-effectiveness analysis of eculizumab versus best supportive care (BSC).
- 1.3 Listing was requested on the basis of a cost-utility analysis of eculizumab versus BSC, a cost-minimisation analysis of ravulizumab versus eculizumab and a cost-utility analysis of ravulizumab (using eculizumab as a proxy) versus BSC.

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

Component	Description
Population	Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are eligible for treatment with eculizumab under the Life Saving Drugs Program (LSDP)
Intervention	Eculizumab (intravenous infusion every 2 weeks; maintenance dosing) or ravulizumab (intravenous infusion every 8 weeks; maintenance dosing)
Comparator	Eculizumab, best supportive care (BSC)
Outcomes	Eculizumab vs BSC: - Transfusion avoidance, haemolysis, breakthrough haemolysis, quality of life, and survival Ravulizumab vs eculizumab: - Transfusion avoidance, haemolysis; breakthrough haemolysis; quality of life, stabilised haemoglobin Ravulizumab vs BSC: - Transfusion avoidance, haemolysis, breakthrough haemolysis, quality of life, and survival
Clinical claim	Eculizumab is superior in terms of efficacy and inferior in terms of safety compared to BSC. Ravulizumab is non-inferior in terms of efficacy and safety compared to eculizumab. Ravulizumab is superior in terms of efficacy and inferior in terms of safety compared to BSC.

Source: Table 1.2, p9 of the resubmission

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. The requested PBS listing in the resubmission pertains to higher strength ravulizumab (100 mg/mL) formulations, which are available in 300 mg in 3 mL and 1,100 mg in 11 mL vials. The TGA approved the higher strength formulations in March 2021.
- 2.2 Eculizumab was TGA registered on the 20 March 2009 for the treatment of patients with PNH to reduce haemolysis and was approved for TGA registration for treatment of patients with atypical Haemolytic Uraemic Syndrome (aHUS) on 3 October 2012.

Previous PBAC consideration

- 2.3 The outstanding matters of concern from the previous July 2020 PBAC meeting are summarised in the table below.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
The PBAC considered that ravulizumab was non-inferior to eculizumab for short-term outcomes including transfusion avoidance, haemolysis (measured by LDH change), breakthrough haemolysis (BTH), quality of life and stabilised haemoglobin (para 7.3, ravulizumab PSD, July 2020 PBAC meeting).	The clinical claim of superiority for ravulizumab versus eculizumab in terms of BTH was removed. The resubmission presented a cost-minimisation analysis of ravulizumab and eculizumab based on a claim of non-inferior efficacy and safety.
The PBAC considered that due to the lack of long-term follow-up data available for ravulizumab, it was uncertain whether a patient's lifespan would be substantially extended as a direct consequence of use of ravulizumab (para 7.8, ravulizumab PSD, July 2020 PBAC meeting).	The resubmission provided additional analyses based on 24-month follow-up data from the extension periods of the key trials (301 and 302) for ravulizumab for outcomes including transfusion avoidance, haemolysis (measured by LDH change), BTH, quality of life and stabilised haemoglobin

Public Summary Document – July 2021 PBAC Meeting

Matter of concern	How the resubmission addresses it
<p>The PBAC noted the submission’s claim of non-inferior survival of ravulizumab versus eculizumab, and superior survival versus BSC, was entirely based on the available survival data for eculizumab, an assumption that non-inferiority for measured surrogate outcomes may be extended to survival and that ravulizumab is a pharmacological analogue of eculizumab. The PBAC considered that it may not be reasonable to assume that the superior survival benefit previously accepted for eculizumab versus BSC can be applied to ravulizumab in the absence of any long-term survival data for ravulizumab. Moreover, the magnitude of any survival benefit of eculizumab versus BSC is in itself unclear, given the lack of contemporary data for BSC survival outcomes (para 7.4, ravulizumab PSD, July 2020 PBAC meeting).</p>	<p>The resubmission presented new survival data for eculizumab versus BSC based on the following:</p> <ul style="list-style-type: none"> - Systematic review of published natural history of PNH studies and survival in eculizumab treated and untreated patients. - Survival comparison of eculizumab ever-treated and eculizumab never-treated patients based on data from the International PNH registry.
<p>The PBAC considered there was substantial uncertainty in the modelled economic analysis of ravulizumab (using eculizumab as a proxy) versus BSC and considered the model structure lacked face validity and was therefore not reliable for decision-making (para 7.10, ravulizumab PSD, July 2020 PBAC meeting). The PBAC considered that any resubmission should be a major resubmission and require a new economic model, and potentially, a significant price reduction (para 7.17, ravulizumab PSD, July 2020 PBAC meeting).</p>	<p>The model structure in the resubmission was fundamentally unchanged, however, there were no transitions to spontaneous remission in the base case. The model was essentially a survival model with two health states, ‘alive with PNH’ and ‘dead’.</p> <p>The proposed price of ravulizumab (\$ [REDACTED]) was revised based on a cost-minimisation analysis versus eculizumab, using the April 2021 price of eculizumab on the LSDP (\$ [REDACTED] per 300 mg vial).</p>
<p>The PBAC considered that the magnitude of survival benefit attributed to ravulizumab (using eculizumab as a proxy) versus BSC in the model was optimistic and implausible, with most of the outcomes accrued in the extrapolated period. The applicability of the Kelly 2011 retrospective study to represent contemporary BSC was unclear, and likely underestimated survival in the BSC arm (para 7.11, ravulizumab PSD, July 2020 PBAC meeting).</p>	<p>The resubmission used revised clinical inputs based on an unpublished analysis of the sponsor’s PNH registry data to inform modelled survival for eculizumab versus BSC. The economic model for ravulizumab versus BSC was reliant on the same data (based on eculizumab).</p>
<p>The PBAC considered that the utility values assigned to patients treated with ravulizumab lacked face validity, considering the need for a utility cap in the ravulizumab arm suggested the application of utility values in the model was inappropriate (para 7.12, ravulizumab PSD, July 2020 PBAC meeting).</p>	<p>The resubmission used revised utility inputs with the removal of utility gain associated with reduced infusion frequency.</p>
<p>The PBAC considered the net cost of treatment with ravulizumab in the financial estimates was highly uncertain and should be re-examined in any resubmission (para 7.15, ravulizumab PSD, July 2020 PBAC meeting).</p>	<p>A revised market-share approach was used to estimate the financial impact of ravulizumab based on estimated number of eculizumab patients on the LSDP and patients treated with eculizumab in clinical trials.</p>
<p>The PBAC noted the submission proposed a risk sharing arrangement to manage uncertainty in cost to Government should ravulizumab be listed on the PBS, with the proposal based on the assumption ravulizumab could be included in the existing Deed of Agreement in place for eculizumab on the LSDP. The PBAC considered the estimated patient numbers and proposed payment thresholds were over-estimated and higher than justified by current LSDP expenditure, even accounting for patients currently receiving treatment through clinical trials (para 7.16, ravulizumab PSD, July 2020 PBAC meeting).</p>	<p>The proposed risk sharing arrangement included updated Commonwealth Payment Thresholds based on a revised market-share approach to estimate the eligible patient population, which [REDACTED] and [REDACTED] the terms of the existing Deed of Agreement for eculizumab (assuming [REDACTED]). The resubmission also proposed the [REDACTED].</p>

Source: Table 1.1, p3 of the resubmission

Abbreviations: LDH, lactate dehydrogenase; LSDP, Life Saving Drugs Program

2.4 The PBAC previously noted that eculizumab was subject to a review by the LSDP Expert Panel and the recommendation to the Chief Medical Officer at the end of that review may include advice on the possibility of re-considering eculizumab for the PBS. As such the ravulizumab consideration for PBS listing would be impacted by this outcome (para 7.18, ravulizumab Public Summary Document (PSD), July 2020 PBAC meeting).

2.5 The Draft Final Review Report (May 2020) of eculizumab for PNH (referred to as the LSDP report) was provided with the resubmission. The resubmission noted that the LSDP Expert Panel met in October 2020, however, the outcome of this meeting was not known to the sponsor at the time of the resubmission.

2.6 The PBAC and ESC received the Expert Panel Recommendations for the LSDP Review of PNH and sponsor comment from the Department for noting. The PBAC noted that Term of Reference 2 (ToR 2) of the LSDP Review of PNH was to ‘Review evidence for the management of PNH and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of eculizumab on the program’. In addition, the PBAC noted ToR 5 was to ‘Assess the value for money of eculizumab under the current funding arrangements by evaluating the benefit of the drug’s treatment outcomes and cost’. The PBAC considered the following recommendations for ToR 2 and ToR 5 to be of particular interest:

- Recommendation 2 (ToR 2): The Expert Panel (EP) advised that [REDACTED]
- Recommendation 5 (ToR 5): The EP noted that [REDACTED]
- Recommendation 6 (ToR 5): The EP recommended [REDACTED]



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

3 Requested listing

- 3.1 While the resubmission acknowledged the potential for both eculizumab and ravulizumab to be considered for PBS listing, there were no proposed PBS restrictions for eculizumab.
- 3.2 The resubmission requested listing of formulations of higher strength ravulizumab 100 mg/mL (available in 300 mg in 3 mL and 1,100 mg in 11 mL vials), compared to the lower strength 10 mg/mL (300 mg in 30 mL vial) requested previously.
- 3.3 The requested restrictions have been revised from the previous submission, incorporating the Secretariat’s edits during the July 2020 PBAC consideration of ravulizumab (para 3.1, ravulizumab PSD, July 2020 PBAC meeting). The category of listing has been amended from a Section 100 – Highly Specialised Drugs Program (Community Access) Program listing to a regular Section 100 – Highly Specialised Drugs Program (Public/Private hospital) Program listing due to complexities with the method of administration. This was appropriate. 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	Max. qty packs	Max. qty units	No. of Rpts	Dispensed price for maximum quantity (effective price)	Available brands
RAVULIZUMAB						
Ravulizumab 300 mg/3 mL injection, 3 mL vial	NEW	1	1	2	Public hospital: \$ [REDACTED] (\$ [REDACTED]) Private hospital: \$ [REDACTED] (\$ [REDACTED])	Ultomiris
Ravulizumab 1.1 g/11 mL injection, 11 mL vial	NEW	1	1	2	Public hospital: \$ [REDACTED] (\$ [REDACTED]) Private hospital: \$ [REDACTED] (\$ [REDACTED])	Ultomiris
Restriction Summary [new] 4567						
Category / Program: Section 100 – Highly Specialised Drugs Program						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate assessment by Services Australia						
Episodicity: blank						
Severity: blank						
Condition: Paroxysmal nocturnal haemoglobinuria (PNH)						

Public Summary Document – July 2021 PBAC Meeting

Indication: Paroxysmal nocturnal haemoglobinuria (PNH)
Treatment Phase: Initial treatment- Initial 1 (new patient)
Clinical criteria:
Patient must have a diagnosis of PNH established by flow cytometry., Patients must not have a small granulocyte clone size: (a granulocyte clone size below 10%)
AND
Patient must have a raised lactate dehydrogenase value at least 1.5 times the upper limit of normal.
AND
Patient must have received/will receive a meningococcal vaccination at the time of initiating treatment that is documented in the patient's medical records
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 red blood cell measurements not exceeding 70 g/L in the absence of anaemia symptoms; OR
<i>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</i>
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
<i>Patients must not have a small granulocyte clone size (a granulocyte clone size below 10%).</i>
AND
Patient must not have aplastic anaemia (having at least 2 of the following indicates the presence of aplastic anaemia: neutrophil count below 0.5 x 10 ⁹ /L, platelet count below 20 x 10 ⁹ /L, reticulocytes below 25 x 10 ⁹ /L, severe bone marrow hypocellularity).
AND
Patient must not have another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by therapy (e.g. acute myeloid leukaemia/ high-risk myelodysplastic syndrome).
AND
Patient must not have another medical condition that might reasonably be expected to compromise a response to therapy.
AND
Patient must not be currently participating in a clinical trial.
Treatment criteria:
Must be treated by a haematologist or in consultation with 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:
Patients must be aged 18 years or older
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).

Public Summary Document – July 2021 PBAC Meeting

<p>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</p>
<p>Administrative advice: No increase in the maximum number of repeats may be authorised.</p>
<p>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.</p>

<p>Category / Program: Section 100 – Highly Specialised Drugs Program</p>
<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
<p>Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate assessment by Services Australia</p>
<p>Episodicity: blank</p>
<p>Severity: blank</p>
<p>Condition: Paroxysmal nocturnal haemoglobinuria (PNH)</p>
<p>Indication: Paroxysmal nocturnal haemoglobinuria (PNH)</p>
<p>Treatment Phase: Initial treatment- Initial 2 (switching from eculizumab)</p>
<p>Clinical criteria:</p>
<p>Patient must be receiving supply of eculizumab under the Australian Government's Life Saving Drugs Program eligibility criteria for this condition <i>at the time of making this application.</i></p>
<p>AND</p>
<p>Clinical criteria:</p>
<p><i>Patient must currently be eligible to continue treatment with eculizumab under the Australian Government's Life Saving Drugs Program eligibility criteria for this condition</i></p>
<p>Clinical criteria:</p>
<p><i>Patient must be up to date with meningococcal vaccination in accordance with the current version of the Australian Immunisation Handbook.</i></p>
<p>AND</p>
<p>Treatment criteria:</p>
<p>Must be treated by a haematologist or in consultation with a haematologist; or Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details.</p>
<p>Population criteria:</p>
<p>Patients must be aged 18 years or older</p>
<p>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).</p>
<p>Administrative advice:</p>
<p>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:</p>

Public Summary Document – July 2021 PBAC Meeting

Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative advice: 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.
Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate assessment by Services Australia
Episodicity: blank
Severity: blank
Condition: Paroxysmal nocturnal haemoglobinuria (PNH)
Indication: Paroxysmal nocturnal haemoglobinuria (PNH)
Treatment phase: Continuing treatment
Clinical criteria: Patient must have previously received LSDP subsidised treatment with this drug for this condition, OR <i>Patient must have previously received PBS-subsidised treatment with this drug for this condition.</i>
Grandfathering: Patient must have received non-LSDP PBS subsidised treatment with this drug for this condition as part of the clinical trial programme prior to listing date (<i>separate grandfather treatment listing to be proposed by Secretariat for such patients; details still to be determined</i>)
AND
Clinical criteria: Patient must not be currently participating in a clinical trial
AND
Clinical criteria: Patient must demonstrate clinical improvement or stabilisation of the condition based on clinical data on the following monitoring requirements provided every 12 months (<i>further refinement by the Secretariat would be required with respect to how many need to be met, what values/outcomes must be met, what evidence is acceptable, etc.</i>): haemoglobin (Hb); platelets; white cell count; reticulocytes; neutrophils; granulocyte clone size; lactate dehydrogenase (LDH); urea and electrolytes; eGFR; iron studies; thrombosis; transfusions; anaemia; pulmonary insufficiency; renal insufficiency; smooth muscle spasm, transfusion history; quality of life (narrative including fatigue); PNH related medications; anecdotal information from treating physician; other conditions/diagnosis; vaccination date.
Clinical criteria: <i>Patient must be up to date with meningococcal vaccination in accordance with the current version of the Australian Immunisation Handbook.</i>
Prescribing instructions: Patient eligibility for ongoing treatment is to be reviewed every 12 months. The treating physician must submit an application for continued subsidised treatment through the LSDP*.
Population criteria: Patients must be aged 18 years or older
Prescribing instructions: <i>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).</i>
Administrative advice:

a mix. It was also unclear whether the conditions listed in the LSDP exclusion criteria for eculizumab (small granulocyte clone size, development of aplastic anaemia, presence of another life-threatening or severe disease where long-term prognosis is unlikely to be influenced by therapy, another medical condition which may compromise response to therapy) need to be added to the clinical criteria.

- 3.8 The resubmission estimated that there are currently < 500 Australian patients treated with ravulizumab through participation in the sponsor's (< 500 patients) and non-sponsor's (< 500 patients estimated) clinical trials. The sponsor requested grandfathering provision for these patients. The resubmission claimed that these patients would meet the current LSDP eligibility criteria for eculizumab and would therefore also meet the criteria in the proposed restriction for ravulizumab. Thus, no separate grandfathering restriction would be required. No formal assessment of these patients against the LSDP eligibility criteria was provided in the resubmission.

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, generally in their 30s or 40s. 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 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.
- 4.3 In 2010, the PBAC accepted that patients with classic PNH had a significant reduction in age-specific life expectancy (Section 11, eculizumab PSD, July 2010 PBAC meeting). Previously published data suggested trends of improved life expectancy over time for patients with PNH, given improvements in modern supportive treatments (de Latour 2008). More recent data suggest changes in prognosis over time, with differences in risk of thromboembolic events and mortality between subtypes of PNH (classic PNH, aplastic anaemia PNH, intermediate PNH) (Socie 2016).
- 4.4 Ravulizumab, a new 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 intravenous infusion. The regimen starts with a loading dose, followed two weeks later with a maintenance dose, and then ongoing maintenance

dosing every 8 weeks, and therefore has a lower treatment burden than eculizumab (dosing every 2 weeks).

- 4.5 Ravulizumab is positioned as an alternative treatment to eculizumab for patients with PNH. Patients with PNH who do not meet the criteria for subsidised treatment with eculizumab or ravulizumab receive symptomatic treatment with BSC, such as transfusion of red blood cells, iron/folic acid therapy, steroids, anticoagulants, or immunosuppressive therapies. Patients may also receive BSC as adjunctive therapy to ravulizumab or eculizumab at the discretion of the treating clinician.
- 4.6 The resubmission targeted the subgroup of the PNH population that would meet the current LSDP eligibility criteria for the use of eculizumab, with the exception of the paediatric population (age less than 18 years). The resubmission stated that eligible LSDP patients broadly reflect patients with classic PNH, also known as haemolytic PNH; and patients with PNH in the setting of another specified bone marrow disorder or subclinical PNH would not be eligible for treatment.

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

5 Comparator

- 5.1 The resubmission nominated eculizumab as the main comparator for ravulizumab, as the therapy most likely to be replaced in practice. The PBAC previously considered that eculizumab, subsidised through the LSDP, was the appropriate primary comparator (para 7.2, ravulizumab PSD, July 2020 PBAC meeting).
- 5.2 Best supportive care (BSC) was nominated as a secondary comparator to determine the cost-effectiveness of a PBS listing for ravulizumab and eculizumab, as there is currently no PBS-listed medicine specifically for the treatment of patients with PNH. The PBAC previously stated that the inclusion of BSC as a secondary comparator was an appropriate way to determine the cost-effectiveness of a PBS listing for ravulizumab, however, it was noted all data comparing ravulizumab to BSC was indirect, via comparison of eculizumab against BSC (para 7.2, ravulizumab PSD, July 2020 PBAC meeting). The resubmission presented cost-effectiveness analyses for both C5 inhibitors (eculizumab and ravulizumab) versus BSC based on the same economic model, which is reliant on eculizumab survival data.
- 5.3 During the evaluation, it was noted that there are multiple therapies for PNH in late-stage development including eculizumab biosimilars, subcutaneous ravulizumab, pegcetacoplan and crovalimab. The current status of these drugs in the Australian setting was unknown and therefore these therapies were not considered further.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, how eculizumab is currently used in practice and the clinical benefit of the greater disease control achieved with ravulizumab as a longer-acting treatment. The clinician also noted the reduced treatment burden and improved quality of life for patients provided by the need for an intravenous infusion every eight weeks with ravulizumab versus every two weeks with eculizumab. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (52), health care professionals (9) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment including the potential for improved disease control and quality of life with the longer-acting ravulizumab.

6.3 The PBAC noted the advice received from the PNH Support Association of Australia (PNHSAA) clarifying the likely use of ravulizumab in clinical practice. The PBAC specifically noted the advice that the convenience of eight weekly infusions of ravulizumab may result in improvements in quality of life for patients with PNH, with flow on benefits to their respective dependents and carers.

Clinical trials

6.4 The resubmission was based on the following:

- Two head-to-head randomised non-inferiority trials comparing ravulizumab to eculizumab, Trial 301 (treatment-naïve patients) and Trial 302 (previously stable on treatment with eculizumab). A supportive post-hoc subgroup analysis of patients meeting eligibility criteria for eculizumab via the LSDP was conducted for patients in Trial 301. This was previously considered by the PBAC.
- Two indirect comparisons of ravulizumab and BSC/placebo were presented, one based on the meta-analysed results of the two ravulizumab trials (Trials 301 and 302) and one placebo-controlled eculizumab trial (TRIUMPH), with eculizumab as a common reference; and a second using the results from Trial 301 only compared to TRIUMPH, with eculizumab as common reference (treatment-naïve population). This was previously considered by the PBAC.
- Additional analyses based on 24-month follow-up data from the extension periods of the key trials (301 and 302) for ravulizumab. This has not previously been considered by the PBAC.
- Eculizumab survival data based on a review and assessment of survival studies considered in the previous ravulizumab submission and in the LSDP review, as well

as new studies identified through literature searches. The review includes data previously considered by the PBAC (in previous eculizumab and ravulizumab submissions) as well as new studies not previously considered by the PBAC.

- An unpublished analysis of survival of eculizumab ever-treated patients (Australian cohort and International cohort) versus eculizumab never-treated patients in the International PNH registry, reflecting new data that represent contemporary BSC survival outcomes. These data were used in the base case of the economic model comparing both C5 inhibitors (eculizumab and ravulizumab) versus BSC. This has not previously been considered by the PBAC.

6.5 Details of the trials presented in the resubmission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ravulizumab vs eculizumab		
Trial 301	CSR ALXN1210-PNH-301. A Phase 3, Randomized, Open-Label, Active-Controlled Study Of ALXN1210 Versus Eculizumab In Complement Inhibitor-Naive Adult Patients With Paroxysmal Nocturnal Haemoglobinuria (PNH)	May 2018
	CSR ALXN1210-PNH-301. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naive adult patients with paroxysmal nocturnal haemoglobinuria (PNH)	May 2019
	Addendum to clinical study report (52-week data update)	
	Lee JW, de Fontbrune FS et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study.	<i>Blood</i> 2019; 133(6): 530-539
	Lee JW, Bachman ES, et al. Immediate, complete and sustained inhibition of C5 with ALXN1210 reduces complement-mediated hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH): Interim analysis of a dose-escalation study.	<i>Blood</i> 2016; 128:2428
Schrezenmeier H, Gandhi S, Kulasekararaj A, et al. One-year efficacy of ravulizumab (ALXN1210) in adult patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibitors	<i>British Journal of Haematology</i> 2020b; 189:137-8	
Schrezenmeier H, Kulasekararaj A, Mitchell L, et al. One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study.	<i>Therapeutic Advances in Hematology</i> 2020c; 11	
Trial 302	CSR ALXN1210-PNH-302. A Phase 3, Randomized, Open-Label, Active-Controlled Study Of ALXN1210 Versus Eculizumab In Adult Patients With Paroxysmal Nocturnal Haemoglobinuria (PNH) Currently Treated With Eculizumab.	May 2018
	CSR ALXN1210-PNH-302. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal haemoglobinuria (PNH) currently treated with eculizumab. Addendum to clinical study report (52-week data update)	May 2019
	Kulasekararaj, A., et al. One-Year Efficacy and Safety from a Phase 3 Trial of Ravulizumab in Adult Patients with Paroxysmal Nocturnal Haemoglobinuria Receiving Prior Eculizumab Treatment.	<i>Blood</i> 2019; 134 (Supplement 1): 2231
	Kulasekararaj AG, Hill A, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: The 302 study.	<i>Blood</i> 2019; 133(6): 540-549.
	Kulasekararaj A, Mitchell L, Hill A, et al. One-year efficacy and safety from a phase 3 trial of ravulizumab in adult patients with paroxysmal nocturnal hemoglobinuria receiving prior eculizumab treatment.	<i>British Journal of Haematology</i> 2020; 189:138-9
Peipert JD, Kulasekararaj AG, Gaya A, et al. Patient preferences and quality of life implications of ravulizumab (every 8 weeks) and eculizumab (every 2 weeks) for the treatment of paroxysmal nocturnal hemoglobinuria.	<i>PLoS ONE</i> 2020; 15 (9 September)	
Eculizumab vs BSC/placebo		
TRIUMPH	CSR C04-001. TRIUMPH: A Haemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Haemoglobinuria Patients	July 2006
	Hillmen P, et al. The complement inhibitor eculizumab in paroxysmal nocturnal haemoglobinuria.	<i>New England J Med</i> 2006; 355(12): 1233-1243.
	Hill A, et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria.	<i>British Journal of Haematology</i> 2010; 149(3): 414-425.

Source: Table 2.10, p55 of the resubmission

6.6 The key features of the randomised trials are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Ravulizumab vs eculizumab						
Trial 301	246	Multicentre, randomised, open label, active controlled noninferiority trial 26 weeks	Unclear	Treatment naive	Transfusion avoidance, LDH normalisation, BTH, stabilised haemoglobin, change in FACIT-fatigue score, % change in LDH. EORTC QLQ-C30	Rate of RBC transfusions
Trial 302	195	Multicentre, randomised, open label, active controlled noninferiority trial 26 weeks	Unclear	Clinically stable with eculizumab treatment	Transfusion avoidance, % change in LDH, BTH, stabilised haemoglobin, change in FACIT-fatigue score, EORTC QLQ-C30	Not used
Meta-analysis	441	Included Trial 301 and trial 302				Not used
Indirect comparison: Eculizumab vs placebo/best supportive care, eculizumab common reference						
TRIUMPH	87	Multicentre, randomised, double blind, placebo controlled trial 26 weeks	High	Treatment naive	Haemoglobin stabilization, blood transfusions, transfusion avoidance ^a , LDH AUC, change in FACIT-fatigue score ^a , % change in LDH ^a , EORTC QLQ-C30	EORTC QLQ-C30 scores

Source: Section 2.4, pp69-108 of the resubmission

Abbreviations: AUC, area under the curve; BTH, breakthrough haemolysis; ecu, eculizumab; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase

^a Outcomes included in indirect comparison (transfusion avoidance, change from baseline in FACIT-fatigue score, % change from baseline in LDH).

6.7 There were no long-term studies of survival in patients treated with ravulizumab. Additional two-year data available from the extension periods of the ravulizumab clinical trials were presented in the resubmission, however, these were based on short-term outcomes including transfusion avoidance, haemolysis (measured by LDH change), breakthrough haemolysis (BTH), quality of life and stabilised haemoglobin. No further data were presented in the resubmission that explored the relationship between the treatment effect of ravulizumab on these outcomes with longer term outcomes such as thromboembolism risk and the risk of mortality. The Pre-Sub-Committee Response (PSCR) stated that a post-hoc analysis from the trial 301 extension study, showed that over the 2-year treatment period ravulizumab reduced the risk of major adverse vascular events (MAVE) and thrombosis in patients with PNH who have high disease activity and are at an increased risk of MAVE and thrombosis compared with the two years prior to enrolment. The ESC considered the results reported in this unpublished conference abstract should be interpreted with caution given the analysis was uncontrolled, with limited reporting in the available abstract. The results were also based on a relatively small number of events; in particular, the subgroup with lower LDH levels was small (n=33) with only 1 thromboembolic (TE) event informing the rate of TEs in each of the periods of analysis.

Comparative effectiveness

Ravulizumab trial data

- 6.8 Results from the comparison of ravulizumab and eculizumab for the 26-week outcomes of LDH normalisation, % LDH change from baseline, proportion of patients experiencing transfusion avoidance, breakthrough haemolysis and haemoglobin stabilisation, and change from baseline in quality of life (FACIT-fatigue scale) were previously considered by the PBAC. All efficacy outcomes were within the bounds of the pre-specified non-inferiority margins from the trials, and results indicated non-inferiority of ravulizumab to eculizumab for all measured outcomes.
- 6.9 Change from baseline in EORTC QLQ-C30 scores were included in Trials 301 and 302 as an exploratory outcome, with differences between treatment arms not assessed for non-inferiority. There was limited detail provided in the resubmission, with mean baseline, endpoint and change from baseline in EORTC QLQ-C30 scores not provided, limiting the usefulness of these results. The PBAC previously questioned the appropriateness of EORTC QLQ-C30 scores reported in the trials, noting the instrument is specifically used to assess the health-related quality of life in cancer patients (para 7.7, ravulizumab PSD, July 2020 PBAC meeting).
- 6.10 The ESC noted the resubmission presented additional analyses based on the extension periods of Trials 301 and 302 for transfusion avoidance, LDH normalisation, BTH, stabilised haemoglobin and change from baseline in FACIT-fatigue scores.
- 6.11 Preliminary results from the extension period of both ravulizumab trials suggest that the treatment effect of ravulizumab based on the measured outcomes remained steady through to the 2-year follow-up. Results for mean change from baseline in FACIT-fatigue scores to 2 years were only presented graphically. FACIT-fatigue scores remained steady from Week 26 to 2 years in both treatment arms of Trial 301 and declined gradually in both treatment arms of Trial 302.
- 6.12 Results of the meta-analysed data from Trials 301 and 302 at 26 weeks were similar to the individual trial results for all included outcomes with the exception of breakthrough haemolysis (BTH), with a numerical difference in favour of ravulizumab in terms of number of BTH events. The PBAC previously considered that ravulizumab was non-inferior to eculizumab in terms of BTH (para 7.5, ravulizumab PSD, July 2020 PBAC meeting).
- 6.13 Results of the indirect comparisons of ravulizumab and BSC (using eculizumab as a common reference) were represented in the resubmission for the overall population, comparing the results of the meta-analysis of Trials 301 and 302, and the eculizumab TRIUMPH trial; and the treatment naïve population comparing Trial 301 with the TRIUMPH trial. The results of the indirect comparison suggest that ravulizumab has a statistically significantly better efficacy profile than placebo for the outcomes of transfusion avoidance, percent change in LDH levels, and FACIT-fatigue scores. However, reiterating its advice on the July 2020 submission, the ESC considered that

the robustness of the indirect comparison was hindered by the limited number of comparable outcomes available between the trials, and issues of exchangeability between the two ravulizumab trials and the TRIUMPH trial (para 6.27, ravulizumab PSD, July 2020 PBAC meeting).

Eculizumab survival data

Comparative studies

- 6.14 In the July 2020 ravulizumab submission, the PBAC considered that the availability of new and different data provided across multiple communications relating to ravulizumab and eculizumab (the ravulizumab submission, LSDP review for eculizumab and minor submission response correspondence for eculizumab) confounded the interpretation of survival data presented in the submission (para 6.34, ravulizumab PSD, July 2020 PBAC meeting).
- 6.15 The resubmission conducted an extensive assessment of the applicability of the 30 identified published studies to the population eligible for eculizumab on the LSDP. As a result, survival data in the resubmission were based on 14 studies of PNH with survival outcomes. These included natural history studies, eculizumab treated patients (single-arm studies) and studies comparing eculizumab versus no eculizumab treatment groups (summarised in the table below).

Table 5: Published survival data included in the resubmission

Survival data	Previously considered by the PBAC		Not previously considered by the PBAC
	Previous eculizumab submissions	July 2020 ravulizumab submission	
Natural history of PNH (untreated/BSC)	de Latour 2008 Nishimura 2004 Socie 1996	Jang 2016	Fu 2019 Yenerel 2017
Eculizumab only (single-arm)	Nil	Hill 2012 (abstract) Hillmen 2013	Ninomiya 2016
Eculizumab vs no eculizumab	Nil	Hill 2017b (abstract) Kelly 2011 Loschi 2016	Kang 2020 Kulagin 2018 (abstract)

Source: Table 2.102, p192 of the resubmission

- 6.16 Overall, the resubmission’s approach to study selection was complex and difficult to reproduce given the use of subjective criteria that are typically used in the interpretation of results rather than study selection. Consequently, a number of studies previously considered by the PBAC were excluded (Hillmen 1995, Moyo 2004, Munoz-Linarex 2014 and Socie 2016).
- 6.17 The use of applicability criteria as study selection criteria also resulted in the inclusion of a number of studies that had limited reporting and therefore did not clearly trigger the inclusion/exclusion criteria used in the resubmission (e.g. Hill 2012, Hillmen 2013 and Kulagin 2018 available as abstracts only).

6.18 The risk of bias for all included studies should be considered high due to the use of observational data. All included comparative studies were retrospective in nature with uncontrolled assignment of treatment to patients.

6.19 The assessment of risk of bias was challenging due to the wide range of study designs employed as well as non-standard reporting of key study characteristics. Data sources used in the studies included surveys, patient records, disease registries, health insurance databases and post-marketing surveillance; all of which necessitate the use of tailored methods to define the inclusion/exclusion of patients (e.g. look-back periods, co-morbidities, disease severity, use of other therapies) and outcomes analysis.

6.20 The table below presents an overview of survival estimates for eculizumab and no eculizumab comparative studies included in the resubmission.

Table 6: Overview of survival estimates for eculizumab and no eculizumab comparative studies

Study	Group	N	Data capture	Duration of follow-up, yrs	Age at diagnosis, yrs, median (range)	Diagnostic test	Survival estimates	ECU vs no ECU, HR (95% CI)
Hill 2017b (Global)	ECU	1,534	Before July 2016	Mean 4.2 (SD: 2.6)	Mean baseline: 43	NR	Rate per 100 patient-yrs: 1.13	-
	No ECU	3,058	Before July 2016	Mean 2.7 (SD: 2.1)	Mean baseline: 45	NR	Rate per 100 patient-yrs: 2.19	
Kang 2020 (Korea)	ECU	68	2002-2016	Median 2.5 (0.3-4.1)	51 (19-82)	FC	4-yr: 98.3%	-
	No ECU	244	2002-2016	Median 1.7 (<0.01-4.3)	51 (1-94)	FC	4-yr: 79.7%	
Kelly 2011 (UK)	ECU	79	2002-2010	Max 8	37 (12-79)	FC	5-yr: 95.5%	0.21 (0.05-0.88)
	No ECU	30	1997-2004	Max 7	NR	NR	5-yr: 66.8%	
Kulagin 2018 (Russia)	ECU	114	From 2011	NR	NR	NR	5-yr: 91%	0.23 (0.1-0.52)
	No ECU	89	From 2011	NR	NR	NR	5-yr: 74%	
Loschi 2016 (France)	ECU	123	2005-2014	4.5 (2.5-5.6)	37 (24-49)	FC	6-yr: 92%	-
	No ECU	100	>1985	5.1 (1.8-11.4)	38 (26-51)	Ham and/or FC	6-yr: 80%	0.38 (0.15-0.94))
	No ECU	191	1954-1985	4.5 (2.5-5.6)	38 (27-50)	Ham and/or FC	6-yr: 58%	0.16 (0.07-0.37)

Source: Table 2.106, p210 of the resubmission

Abbreviations: CI, confidence interval; ECU, eculizumab; FC, flow cytometry; HR, hazard ratio; NR, not reported; SD, standard deviation

Note: Studies highlighted in blue have not previously been considered by the PBAC

The results presented in this table were updated during the evaluation to reflect available results in the references provided.

6.21 There were multiple survival estimates presented in the resubmission that could not be validated during the evaluation due to poor documentation. For example, the hazard ratio for the Kang 2020 study referenced in the resubmission (HR 0.11) was not presented in the study publication. The estimate appeared to be inappropriately

derived in the resubmission from Table 2 of Kang (2020) using the multivariate analysis of the unadjusted set of treated and untreated patients (N=1,340) that was used to identify prognostic factors related to survival (the use of ecilizumab no vs yes; HR: 9.318 95% CI (1.28, 67.74); calculated in the resubmission as $1/9.318 = 0.11$) to derive the hazard ratio of ecilizumab vs no ecilizumab.

- 6.22 The majority of the evidence presented in the resubmission has been considered by the PBAC in previous ecilizumab submissions and the July 2020 ravulizumab submission. The PBAC previously noted ecilizumab's survival data varied significantly in relation to duration of follow-up. In July 2020, the PBAC also considered the magnitude of any survival benefit of ecilizumab versus BSC was unclear given the lack of contemporary data for BSC survival outcomes (para 7.4, ravulizumab PSD, July 2020 PBAC meeting).
- 6.23 There was substantial variance in the survival estimates across the included studies in this resubmission which were difficult to interpret and compare. The resubmission stated the assessment of the evidence was challenging due to numerous issues surrounding heterogeneity and applicability to the PBS population (e.g. age of study, study design, population and disease characteristics, and healthcare settings).
- 6.24 However, the resubmission claimed the study by Kang (2020) represented the best evidence from the comparative studies, given the population was broadly applicable to the LSDP population, and the propensity matching on important disease and demographic characteristics of the ecilizumab and untreated cohorts reduced the potential for confounding. The analysis only included patients who were alive from the time of ecilizumab availability (from October 2012), therefore there is risk of selection and immortal time biases (i.e. patients who survived a risk-free period prior to ecilizumab availability). The results of this study were also limited by relatively short follow-up durations for both untreated and treated groups (median duration of 1.7 and 2.5 years respectively).
- 6.25 Overall, the body of evidence for survival should be interpreted with caution as it was difficult to differentiate between survival benefit associated with improvements in BSC over time from treatment benefit associated with ecilizumab. The following are limitations specific to survival analyses conducted in the included studies:
- The use of supportive therapies and overall disease management (diagnosis of concomitant bone marrow disorders and co-morbidities) at baseline and over time were not well reported.
 - Data relating to causes of death and incidence of life-threatening events such as thromboembolisms were sparse.
 - Some studies had overlapping cohorts of treated and untreated patients, with survival analysis based on pre- and post-ecilizumab eras. There is a high risk of immortal time bias given the inclusion of patients in the treated cohort was conditional upon survival during the pre-ecilizumab era (i.e. risk-free period).

- Comparisons of survival between eculizumab and BSC that were conducted using ever-treated and never-treated cohorts should be interpreted with caution due to potential confounders relating to access to treatment (e.g. disease severity, healthcare setting, rare disease treatment coverage).
 - Most survival comparisons were unadjusted for treatment exposure to eculizumab, assuming no relationship between the duration of therapy and mortality. Where treatment exposure was included as a covariate, this was defined as a baseline (fixed effects) rather than a time-varying measure.
 - Adjustments for known prognostic factors were typically conducted using baseline data only, not accounting for time-varying prognostic factors (e.g. thrombotic events, clonal evolution, development of malignancies).
- 6.26 The PSCR argued that the evaluation of published eculizumab survival data included in the resubmission reflected an improved assessment of available sources, which has reduced the magnitude of incremental survival benefit with eculizumab owing to selection of more contemporary BSC data. The ESC noted the resubmission’s approach to study selection was complex and difficult to reproduce (see paragraph 6.13). Despite the inclusion of newer evidence, the ESC considered the data representing BSC remained sparse and largely dated in terms of data collection. The ESC noted the substantial variation in the survival estimates and considered that they should be interpreted with caution due to the high risk of bias, significant heterogeneity between studies and differential durations of follow-up. As such, the ESC agreed with the evaluation that it was difficult to differentiate the survival benefit associated with improvements in BSC over time from the treatment benefit associated with eculizumab based on these published data.

PNH Registry data

- 6.27 The resubmission considered the adjusted survival analysis based on the International PNH Registry data was the best available evidence upon which to establish the magnitude of survival benefit of eculizumab versus BSC.
- 6.28 The International PNH Registry (NCT01374360, estimated enrolment N=5,000) is a prospective, non-interventional, observational study funded by the sponsor. The study started in January 2007 with an estimated completion date of December 2025. Patients of any age with a clinical diagnosis of PNH (by any applicable diagnostic method and/or detectable PNH clone) were eligible for inclusion in the registry, regardless of disease severity, co-morbidities or treatments (past, current or planned).
- 6.29 The primary aim of the registry is to evaluate safety data specific to the use of eculizumab and ravulizumab (C5 inhibitors) over a maximum follow-up period of 13 years. Secondary outcomes include the collection of data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in patients who are treated or untreated with C5 inhibitors. The analysis presented in the resubmission was based on eculizumab-treated patients only, with the resubmission

noting that provision of registry data pertaining to ravulizumab-treated patients can be requested in the future.

- 6.30 The resubmission presented three survival models comparing the survival of the ever-treated (international and Australian) cohorts versus the international never-treated cohort. The resubmission claimed that a propensity-score adjusted comparison was not feasible given the small sample size of Australian patients and presented both unadjusted and adjusted Cox proportional hazards models. The ESC considered that a propensity-score adjusted comparison may have been possible with the cohort sample size. However, the ESC acknowledged that the small number of events (2 deaths) in the Australian ever-treated cohort may limit confidence in the results of this approach.

Table 7: Descriptions of subgroups used in the survival comparison based on PNH registry data

Survival model	Covariates ^a	Group	N	Description
Unadjusted	-	International, ever-treated	1,989 ^b	All patients who were ever treated with eculizumab
		Australian, ever-treated	74	Australian patients who were ever treated with eculizumab on the LSDP
		International, never-treated	227 ^b	All patients who were never treated with eculizumab
Adjusted – with LDH	- treatment group - age - gender - history of BMD - history of TE - LDH ratio $\geq 1.5 \times$ ULN	International, ever-treated	1,295	All patients who were ever treated with eculizumab, selected variables reported
		Australian, ever-treated	51	Australian patients who were ever treated with eculizumab on the LSDP, selected variables reported
		International, never-treated	200	All patients who were never treated with eculizumab, selected variables reported
Adjusted - without LDH	- treatment group - age - gender - history of BMD - history of TE	International, ever-treated	1,912	All patients who were ever treated with eculizumab, selected variables reported (except LDH ratio)
		Australian, ever-treated	72	Australian patients who were ever treated with eculizumab on the LSDP, selected variables reported (except LDH ratio)
		International, never-treated	200	All patients who were never treated with eculizumab, selected variables reported (except LDH ratio)

Source: Table 2.105, p208 of the resubmission

Abbreviations: BMD, bone marrow disorder; LDH, lactate dehydrogenase; TE, thromboembolism

^a Baseline values used in regression models

^b 1 patient in each cohort had missing time/duration variables

The population used in the base case of the economic model is highlighted in orange

- 6.31 The data used in the resubmission appeared to be based on a subgroup of all patients enrolled in the registry (N=4,948 as of July 2017; Schrezenmeier 2020a), however, this could not be validated during the evaluation due to poor documentation.
- 6.32 There was limited detail on methods of data collection that is typically reported for retrospective analysis of observational data. Apart from a 5 October 2020 data cut-off date, no detail was provided on patient eligibility, look-back period, inclusion/exclusion criteria, median duration of follow-up, and handling of missing data. The ESC noted that paragraph 6.28 provided a small amount of information on patient eligibility criteria.

- 6.33 No justification was provided for the limited selection of variables in the regression models. Published studies have used a range of other baseline (e.g. transfusion dependence, age at diagnosis, PNH classification) and time-varying factors (e.g. eculizumab use, bone marrow transplant, anticoagulants, blood transfusions, thrombotic events) in adjusted survival models (Loschi 2016, Socie 2016, Kang 2020).
- 6.34 The resubmission defined baseline as the date of eculizumab initiation for the treated cohorts and the date of registry enrolment for the never-treated cohort. The ESC agreed with the evaluation that this approach introduces the risk of immortal time bias, in favour of the ever-treated cohorts, as patients had to survive a risk-free period prior to initiation of eculizumab treatment.
- 6.35 The resubmission noted that 30-54% of patients in the ever-treated cohorts had missing LDH data at baseline, therefore two regression models were fitted (with and without LDH). The loss of data with the inclusion of the LDH variable was significant. It was unclear whether the patient populations in the adjusted models were similar to the unadjusted population as the characteristics were not presented in the resubmission. The ESC considered the measurement of serum LDH levels represented routine medical practice in relation to the diagnosis of PNH and assessment of chronic haemolysis and was concerned that such data were not available for all patients in the PNH registry.
- 6.36 Based on the unadjusted dataset (N=2,218), the resubmission acknowledged that there were differences in characteristics between the ever-treated and never-treated cohorts that may affect survival outcomes. Differences included age at diagnosis, history of bone marrow disorder and history of major adverse vascular events or thrombosis. There were also differences in the geographic region and race distribution between the international ever-treated and never-treated cohorts that may indicate differences in treatment accessibility associated with different healthcare systems.
- 6.37 No treatment details of eculizumab (dose, duration of therapy) or supportive therapies (e.g. steroids, immunosuppressants, anticoagulants, blood transfusions) were provided in the resubmission.
- 6.38 The results of the PNH registry analysis are presented in the table and figure below.

Table 8: Survival estimates for ever-treated and never-treated cohorts of the International PNH Registry

Model	Cohort	N	Patients at risk	1 yr	2 yr	3 yr	5 yr	8 yr	Number of deaths
Unadjusted	International ever-treated	1,989	n	1,788	1,646	1,477	1,092	512	127
			% alive	99%	99%	98%	95%	91%	
	Australian ever-treated	74	n	67	64	62	51	24	2
			% alive	100%	100%	100%	98%	96%	
	International never-treated	227	n	148	110	84	41	14	33
			% alive	93%	84%	82%	80%	73%	
Adjusted with LDH	International ever-treated	1,295	% alive	99%	99%	98%	96%	95%	77
	Australian ever-treated	51	% alive	99%	99%	98%	98%	97%	2
	International never-treated	200	% alive	94%	88%	86%	83%	77%	29
Adjusted without LDH	International ever-treated	1,912	% alive	99%	99%	98%	97%	94%	124
	Australian ever-treated	72	% alive	99%	98%	98%	98%	97%	2
	International never-treated	200	% alive	95%	89%	88%	85%	79%	29
Hazard ratio (95% CI)									
Model		Australia ever-treated vs international never-treated				International ever-treated vs international never-treated			
Unadjusted		0.11 (0.03, 0.45)				0.20 (0.14, 0.30)			
Adjusted with LDH		0.10 (0.01, 0.78)				0.29 (0.18, 0.46)			
Adjusted without LDH		0.14 (0.03, 0.64)				0.28 (0.19, 0.43)			

Source: Table 2.107, p212 and Attachment 4 of the resubmission

Abbreviations: LDH, lactate dehydrogenase

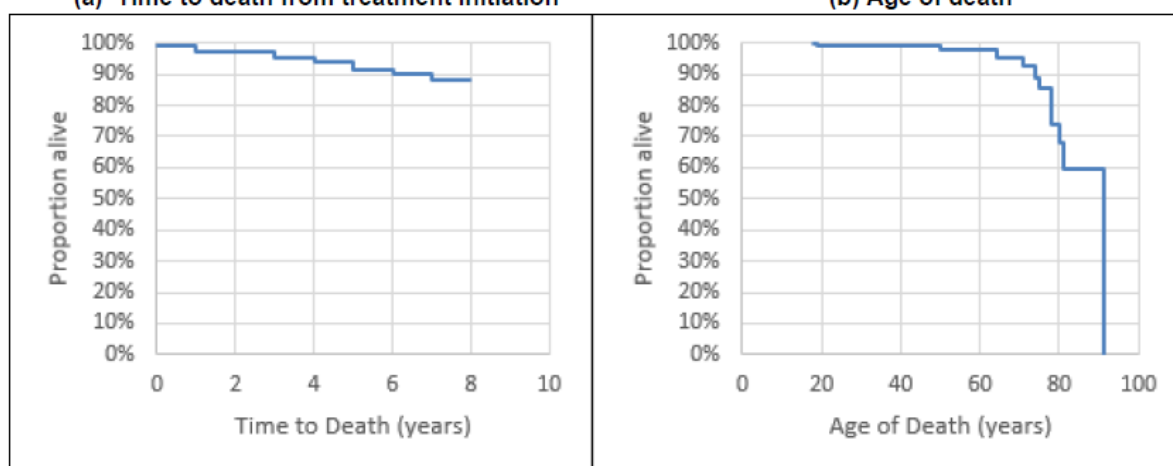
The population used in the base case of the economic model is highlighted in orange.

6.39 The ESC agreed with the evaluation that the results suggest that patients who were ever treated with eculizumab had improved survival compared with patients who were never treated with eculizumab. The results also indicate a greater improvement in survival when comparing the Australian ever-treated cohort with the international never-treated cohort, than comparisons between the international ever-treated and international never-treated cohorts. However, the ESC considered these results should be interpreted with caution due to limited detail provided regarding data collection, heterogeneity between treatment groups, lack of treatment details and risk of bias (selection and immortal time biases). The PBAC noted the reported hazard ratios adjusted with and without LDH were relatively consistent within the Australian ever-treated versus international never-treated and international ever-treated versus international never-treated cohorts.

6.40 Based on the survival curves constructed for each cohort, there appear to be differences in duration of follow-up, with a maximum of 8 years reported for the Australian ever-treated cohort but up to 13 years in the international cohorts. The reasons for this difference were not provided in the resubmission.

- 6.41 The robustness of the data at the tail-end of the curves for the subgroups used in the regression models was unclear as the number of patients remaining at risk was not provided.
- 6.42 The eculizumab survival data reported in the LSDP review (May 2020 draft report) were not considered in the resubmission. The resubmission noted the review included a comparison of modelled survival curves of eculizumab ever treated patients versus natural history, however, the analysis appeared to use time on treatment data for the eculizumab arm rather than time to death. The LSDP review (May 2020 draft report) provided an analysis of unadjusted survival data, which was presented during the evaluation (see Figure 1). The evaluation considered a naïve comparison of these data with the PNH registry analyses may be useful given the Australian cohort in the resubmission’s analysis is a subgroup of patients treated on the LSDP.

Figure 1: Time to death from treatment initiation and age of death, LSDP patient-level data (2011 to 2019)
(a) Time to death from treatment initiation **(b) Age of death**



Source: Figure 71, p551 of the draft report for the LSDP review of PNH (May 2020) provided in the resubmission

Note: The LSDP review report notes limitations with the time to death from treatment initiation analysis that may be subject to confounding, particularly if there is a significant delay between diagnosis and commencement of eculizumab treatment.

- 6.43 The results show approximately 95% 5-year survival and slightly less than 90% 8-year survival in patients ever treated with eculizumab, over a maximum follow-up of 8 years. The median age of death was 77 years (Table 6, p 20 of the May 2020 LSDP Review of PNH report), suggesting the majority of patients died at an older age. Survival rates of these patients appeared lower than results from the PNH registry analysis. The PSCR refuted the usefulness of this comparison arguing that the survival analyses included in the LSDP review appeared to have considered treatment discontinuations as being surrogates for death which may not be appropriate given patients could cease eculizumab treatment to move to a clinical trial. In addition, the PSCR argued that the survival data may have been affected by patients who lived with PNH for a long time before finally initiating LSDP-funded eculizumab meaning they may be older with more advanced PNH. The PSCR acknowledged that the same bias may be evident in the employed registry data but argued that it may be less so given the longer follow up and larger sample size of the PNH registry.

- 6.44 It was unclear whether the subgroup of Australians ever treated in the PNH registry were similar to the LSDP population due to a lack of publicly available data (only age of enrolment into each program was available for comparison). The results for the Australian ever treated cohort were based on 2 deaths and a relatively small number of patients (74 in the unadjusted analysis and 51 in the adjusted with LDH model). The number of deaths reported in these subgroups were relatively low compared to the number of deaths reported for patients treated with eculizumab on the LSDP (11 deaths in 150 patients ever treated between 2011 and 2019) (see Table 1, p3 of the draft report for the LSDP review of PNH, May 2020). The pre-PBAC response argued that regardless of which data source is used, the number of deaths reported for patients treated with eculizumab on the LSDP equates to a low proportion (7%) of the ever treated population.
- 6.45 The resubmission claimed that the international cohort who were eligible but never treated with eculizumab are managed on BSC and therefore represent a plausible comparator arm for the eculizumab treated cohorts. There are concerns with the generalisability of the international never-treated cohort to Australian practice given differences in characteristics in terms of geographic region, age at diagnosis and co-morbidities. There are likely to be other patient and healthcare setting factors that influence both choice and access to therapy in the international setting that may not be applicable to Australian practice.

Comparative harms

- 6.46 The most frequently reported adverse events with ravulizumab and eculizumab in the key trials were headache, upper respiratory tract infections, nasopharyngitis and pyrexia. Both treatments were also associated with a higher incidence of serious infections and infusion reactions.
- 6.47 Overall, the rates of adverse events including serious adverse events and adverse events of special interest remained stable or decreased during the 2-year extension period. One patient experienced thrombosis during the randomised period of the trial. Three deaths were reported during the extension period, all of which were unrelated to PNH (lung adenocarcinoma, pulmonary sepsis and acute myeloid leukaemia).
- 6.48 The resubmission claimed the low occurrence of thrombosis (1 event) and high survival rates (99.5% and 99.8% in Trials 301 and 302 respectively) support the plausibility that a patient's lifespan would be extended with the use of ravulizumab. This claim may not be reasonable given the data were based on an uncontrolled safety extension period of the trial with relatively short follow-up.
- 6.49 The resubmission did not present a comparison of safety between ravulizumab and BSC but assumed the likely inferiority of eculizumab to BSC in terms of safety would also apply to ravulizumab. This was reasonable given the similar mechanism of action and similar patterns of adverse events reported in the ravulizumab and eculizumab trials.

- 6.50 The resubmission presented an expanded assessment of harms for ravulizumab. Important identified risks include meningococcal infections, which is directly associated with its mode of action. Important potential risks include serious haemolysis after drug discontinuation in PNH patients, immunogenicity, serious infections and malignancies and hematologic abnormalities in PNH patients. There is no information available on use in pregnant and breast-feeding women.

Benefits/harms

- A benefits/harms summary for the comparison of ravulizumab and eculizumab was not presented as the clinical claim was based on non-inferiority.
- A benefits/harms summary for the comparison of ravulizumab and BSC was not presented as the data were inadequate to reliably quantify the magnitude of comparative benefits and harms of ravulizumab and BSC.

Clinical claim

- 6.51 The resubmission described ravulizumab as non-inferior to eculizumab in terms of efficacy and safety. The PBAC previously considered that ravulizumab is likely to be non-inferior to eculizumab in the short term (para 7.1, ravulizumab PSD, July 2020 PBAC meeting).
- 6.52 Additional 2-year data from the extension periods support maintenance of treatment effect with ravulizumab based on key endpoints in the trials. However, the magnitude of any survival benefit of ravulizumab remains uncertain due to the absence of long-term survival data.
- 6.53 The resubmission's claim of non-inferior survival of ravulizumab compared to eculizumab, and superior survival compared to BSC was entirely based on the available survival data for eculizumab, and an assumption that non-inferiority for measured efficacy outcomes may be extended to survival.
- 6.54 In July 2020, the PBAC considered that it may not be reasonable to assume that the superior survival benefit previously accepted for eculizumab compared to BSC can be applied to ravulizumab compared to BSC, in the absence of any long-term survival data for ravulizumab. Moreover, the PBAC considered the magnitude of any survival benefit of eculizumab compared to BSC is itself unclear, given the lack of contemporary data for BSC survival outcomes (para 7.4, ravulizumab PSD, July 2020 PBAC meeting). The pre-PBAC response for this resubmission argued that acceptance by the PBAC in July 2020 that ravulizumab is non-inferior to eculizumab with respect to clinically relevant efficacy and safety outcomes, coupled with the fact that it is a pharmacological analogue to eculizumab, suggested it was directly plausible that the survival benefits observed with eculizumab relative to BSC could be extended to ravulizumab. The PBAC noted the support for this argument from the clinical expert in the sponsor hearing.

- 6.55 Survival estimates from the published data presented in the resubmission varied significantly and were limited by varying follow-up durations, risk of bias and applicability concerns. The results were difficult to interpret due to substantial heterogeneity in the evidence base. Despite the inclusion of newer studies, the data for BSC remained sparse and largely dated.
- 6.56 New analyses based on data from the International PNH Registry could not be effectively evaluated due to limited detail on methods of data collection and lack of patient characteristics for the subgroup used in the survival model that formed the base case of the economic model. There were additional concerns with the robustness and applicability of the survival estimates due to heterogeneity between treatment arms, lack of treatment details for eculizumab and supportive therapies used, risk of immortal time bias and discrepancies in the number of deaths reported in the PNH registry subgroup treated on the LSDP versus number of deaths reported in the LSDP report analysis.
- 6.57 The PSCR argued that the totality of the evidence (registry or published), along with the LSDP cohort experience, concur that compared to BSC, patients on eculizumab live significantly longer. The ESC, however, considered that the magnitude of survival benefit associated with eculizumab versus BSC remains uncertain due to the extensive caveats associated with the interpretation of available survival data.
- 6.58 Overall, the PBAC considered there was unlikely to be a substantial improvement in the body of evidence relating to BSC given the established place in therapy of complement inhibitors for the treatment of PNH. The PBAC agreed with the sponsor the data from the International PNH Registry was the best available evidence to establish the magnitude of survival benefit versus BSC in this rare condition.
- 6.59 The PBAC considered that while the magnitude of survival benefit associated with eculizumab versus BSC remained uncertain the claim of superior comparative effectiveness was reasonable.
- 6.60 The PBAC considered that the claim of inferior safety of eculizumab compared to BSC was reasonable.
- 6.61 The PBAC considered that the claim of non-inferior comparative effectiveness of ravulizumab versus eculizumab was reasonable.
- 6.62 The PBAC considered the claim of superior comparative effectiveness of ravulizumab versus BSC was uncertain, due to the caveats associated with the interpretation of available data, but reasonable.
- 6.63 The PBAC reiterated the resubmission's claim of non-inferior safety compared to eculizumab and inferior safety compared to BSC was appropriate (para 7.9, ravulizumab PSD, July 2020 PBAC meeting).

Economic analysis

Cost-minimisation analysis (CMA) of ravulizumab and eculizumab

- 6.64 The resubmission assumed that weight-based dosing of ravulizumab administered every 8 weeks is equivalent to fixed dose eculizumab 900 mg administered every 2 weeks. The estimated equi-effective doses over a 52-week maintenance period were:
- Ravulizumab 21,375 mg (3,288 mg x 6.5 infusions) is equivalent to eculizumab 23,400 mg (900 mg x 26 infusions)
- 6.65 The proposed equi-effective doses were based on the maintenance treatment phase and consistent with recommended doses in the product information. However, the evaluation highlighted that the CMA should be conducted over a two year period for consistency with the time horizon chosen for other drugs considered by the PBAC which include loading doses in year one, such as bDMARDs. The estimated equi-effective doses over the first two years of treatment were:
- Ravulizumab 44,616 mg (13.75 infusions including loading dose) is equivalent to eculizumab 47,400 mg (54 infusions).
- 6.66 The estimated dose for ravulizumab was based on weight distributions from the subgroup of Australians in the International PNH registry who were ever treated with eculizumab on the LSDP, with reported weights. The resubmission claimed that the subgroup was more applicable to the PBS population than trial-based estimates. This claim could not be validated due to poor documentation of this subgroup in terms of data collection and characteristics. It was unclear whether the PNH registry subgroup are representative of LSDP treated patients given the number of patients in the dataset was relatively small (N=52) compared with the total number of patients treated on the LSDP (N=150 between 2011 and 2019).
- 6.67 The resubmission included a cost offset based on the yearly difference in IV administration frequencies associated with ravulizumab (6.5 infusions) versus eculizumab (26 infusions). The cost offset per administration (less than 1-hour infusion for both therapies) was \$111.40 based on MBS item 13950 for parenteral administration of one or more antineoplastic agents. The resubmission did not adequately justify the use of an MBS item for chemotherapy medicines. The Manual of Resource Items v5.0 recommends the use of a standard MBS consultation item if there is no specific MBS item for the administration of the proposed drug. Sensitivity analysis using the MBS item 105 for a follow-up specialist visit (\$45) was conducted during the evaluation.
- 6.68 The cost-minimisation analysis from the submission was presented based on effective prices only, as summarised in the table below.

Table 9: Results of the cost-minimisation analysis – 52-week maintenance period

Estimated cost of eculizumab	
Total dose	23,400 mg
Number of vials	78
Cost per vial (LSDP price per vial as of April 2021)	\$ [REDACTED]
Drug cost	\$ [REDACTED]
Number of administrations	26
Cost of administrations	\$2,896
Total cost	\$ [REDACTED]
Estimated cost of ravulizumab	
Number of administrations	6.5
Ravulizumab administration cost	\$724
Total cost of eculizumab minus ravulizumab administration cost	\$ [REDACTED]
Total dose	21,375 mg
Cost per mg	\$ [REDACTED]
AEMP per 300 mg vial (effective price)	\$ [REDACTED]
AEMP per 1,100 mg vial (effective price)	\$ [REDACTED]

Source: 'Cost-minimisation model workbook' Excel workbook of the resubmission

6.69 The price per vial of ravulizumab as calculated above was used in the cost-utility analysis versus BSC.

6.70 The cost-minimisation analysis adjusting the equi-effective doses over the first two years and the cost of administration based on MBS item 105, is presented below.

Table 10: Results of the cost-minimisation analysis over 2 years - based on initial year and subsequent year costs in the economic model

Estimated cost of eculizumab	
Total dose	47,400 mg
Number of vials	158
Cost per vial (LSDP price per vial as of April 2021)	\$ [REDACTED]
Drug cost	\$ [REDACTED]
Number of administrations	54
Cost of administrations (MBS item 105)	\$2,430.00
Total cost	\$ [REDACTED]
Estimated cost of ravulizumab	
Number of administrations	13.75
Ravulizumab administration cost (MBS item 105)	\$618.75
Total cost of eculizumab minus ravulizumab administration cost	\$ [REDACTED]
Total dose	44,616 mg
Cost per mg	\$ [REDACTED]
AEMP per 300 mg vial (effective price)	\$ [REDACTED]
AEMP per 1,100 mg vial (effective price)	\$ [REDACTED]

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

Cost-utility analysis of eculizumab versus best supportive care

6.71 The ravulizumab July 2020 submission presented a cost-utility analysis of ravulizumab versus BSC. Due to the absence of direct comparative data for ravulizumab versus BSC,

the modelled inputs for survival and quality of life were derived using eculizumab data. The submission's approach assumed non-inferiority between ravulizumab and eculizumab in terms of long-term outcomes.

- 6.72 The same approach was used in the resubmission, which presented the same economic model to represent the cost-effectiveness of eculizumab or ravulizumab versus BSC.
- 6.73 Compared to the ravulizumab July 2020 submission, the main changes to the modelled economic evaluation were:
- Revised time horizon.
 - Revised clinical inputs informing modelled survival for eculizumab and BSC.
 - Removal of transitions to the spontaneous remission health state in the base case.
 - Revised utility inputs with removal of utility gain associated with reduced infusion frequency.
 - Updated ravulizumab price based on cost-minimisation analysis versus eculizumab.
 - Revised rates of TE and included treatment costs.
 - Revised frequencies and costs of blood transfusions.
 - Updated drug administration, disease management and co-administered medication costs.
- 6.74 Noting the changes to the modelled economic evaluation outlined in paragraph 6.73, the ESC considered the model structure remained essentially the same as that presented in the ravulizumab July 2020 submission. The ESC reiterated its previous advice that the model structure used in the comparison versus BSC lacked face validity and was unlikely to be reliable for decision making (para 6.63, ravulizumab PSD, July 2020 PBAC meeting). The pre-PBAC response disagreed with the ESC advice arguing the revised model provided flexibility in terms of data selection, allowing the PBAC to explore alternative scenarios in an easy and transparent manner to inform decision making.
- 6.75 The resubmission presented a stepped economic evaluation of eculizumab versus BSC for the treatment of adult patients with PNH who are eligible for treatment on the LSDP (broadly reflecting classic PNH). The economic evaluation was a cost-utility analysis based on modelled survival benefit using an unpublished analysis of observational data from the International PNH registry and other modelled variables.

Table 11: Key components of the economic evaluation

Component	Summary
Treatments	Eculizumab versus best supportive care
Time horizon	60 years in the model base case versus 6.6 years (Australian ever treated) and 12 years (international never treated) follow-up in the PNH registry analysis
Outcomes	Life-years and quality-adjusted life-year (QALY) gained
Methods used to generate results	Markov cohort model
Health states	Alive with PNH, alive in remission (no transitions allowed in the base case) and dead
Cycle length	1 year, half-cycle corrections
Extrapolation	Separately modelled overall survival curves for eculizumab and BSC using parametric distributions over the modelled duration. Models were based on an unpublished PNH registry analysis comparing the Australian ever-treated with eculizumab versus international never-treated with eculizumab cohorts. A survival cap was included based on age-adjusted mortality in the Australian population. 70.0% of the incremental costs; 93.7% of the incremental life years; 83.6% of the incremental QALYs are accrued in the extrapolated period (beyond 6 years)
Health related quality of life	Baseline PNH utility (both arms): 0.756 Eculizumab non-specific disease-related utility gain: 0.093 BSC non-specific disease-related disutility: -0.061 Thromboembolic events disutility (distributed across treatment arms using rates derived from Kelly 2011 and assumptions): -0.0750 Baseline and non-specific disease-related utility changes were based on quality of life scores (EORTC QLQ-C30) from TRIUMPH and SHEPHERD eculizumab studies mapped to utility values (EQ-5D-3L) and assumptions. Utility values were capped at the utility value of the general population.
Discount rate	5% for costs and outcomes, applied annually
Software package	Excel

Source: Table 3.10, p233 and Sections 3.4 to 3.6, pp240-271 of the resubmission

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-3L, EuroQol 5-dimension 3-level quality of life questionnaire; PNH, paroxysmal nocturnal haemoglobinuria

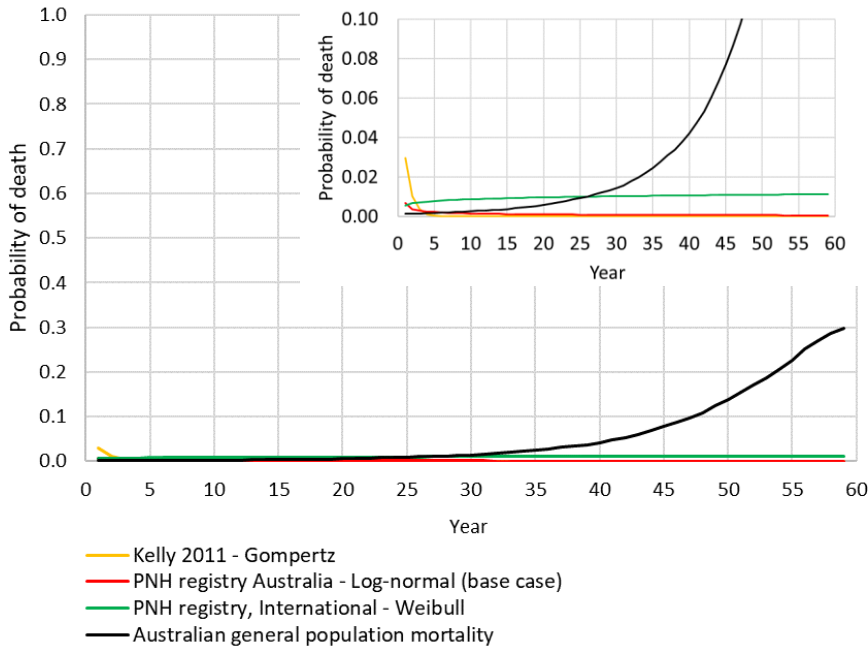
- 6.76 Although there were no major changes to the model structure compared to the previous submission, spontaneous remission is no longer considered in the base case by applying a nil probability for transitions to the ‘alive in remission’ health state (without structural changes to the model). In the base case, the model is effectively a simple survival model with two health states: ‘alive with PNH’ and dead. All patients remaining alive continue to accrue treatment costs (no treatment discontinuation), disease-related costs and consequences.
- 6.77 The resubmission acknowledged that there remained no explicit relationship between treatment effect, the risk of thromboembolic events, blood transfusions and overall survival. The model is based on a simplified approach, applying aggregated costs and consequences to each arm regardless of disease status.
- 6.78 The resubmission argued that there are limited, adequately powered trial data to support a more complex modelling approach that considers the consequences of individual PNH-related complications or symptoms.
- 6.79 Key drivers of the model are summarised in the table below.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Time horizon	The model was based on a lifetime time horizon of 60 years. This was longer than in the previous submission which used a 55-year time horizon but included a younger population (35 years) compared to the population in the resubmission (40 years). While a lifetime horizon is appropriate given the chronic nature of the disease and relatively young age at diagnosis, there were limited data available to support the extrapolation of data to 60 years (maximum follow-up of 6.6 years for the Australian ever treated cohort and 12.8 years for the international never treated cohort).	High, favours eculizumab
Extrapolation	The ESC was concerned with the robustness and applicability of the PNH registry analysis used to inform the base case survival estimates of eculizumab versus BSC. The resubmission explored the use of standard parametric models (exponential, Gompertz, Weibull, log-logistic, log-normal) for the extrapolation of survival data. Survival models were selected based on statistical goodness of fit (Akaike and Bayesian Information Criterion statistics, AIC/BIC) and visual inspection. The choice of survival functions was poorly documented and did not appear to include testing of proportional hazards or use of log-cumulative hazard plots to determine whether hazards are likely to be non-monotonic (log-logistic, log-normal), monotonic (Weibull, Gompertz) or constant (exponential). During the evaluation, plots of extrapolated hazard functions for both treatment arms were constructed to help illustrate the assumed hazards over time (see Figures 2 and 3 below).	High, favours eculizumab
Non-specific disease-related utility gain/loss	<p>The derivation of the baseline and non-specific disease-related utility values was complex and difficult to interpret. The approach included the use of quality of life data from two different trials (e.g. baseline values from the TRIUMPH trial and mean change from baseline scores in the SHEPHERD trial) and the use of cancer-specific instruments (EORTC QLQ-C30) for scoring and mapping. The ESC previously raised significant concerns regarding the methods and applicability of the calculated utility values (para 6.75, ravulizumab PSD, July 2020 PBAC meeting).</p> <p>The inclusion of a utility gain (eculizumab arm) and a utility loss (BSC arm) appeared to be based on non-specific changes in symptoms and/or PNH-related complications and were applied as fixed changes over the modelled duration. The use of these values was inadequately justified in the resubmission and resulted in the eculizumab 'on-treatment' utility estimates exceeding that of the general population.</p> <p>The resubmission applied a utility cap to the 'on-treatment' utility value (baseline + non-specific disease-related utility gain or loss) to ensure that the utility estimates in the model meet face validity. The utility cap was triggered from Year 35+ in the model, where the utility value for eculizumab treated patients exceeded estimates for the age-matched general population. The ESC previously considered that the need for a utility cap suggested the application of utility values in the model was inappropriate; noting that even with this forced cap, it is required to assume that eculizumab treated patients who still have PNH have the same quality of life as the general population. This assumption was inadequately justified given these patients have a life-threatening disease and may still experience lifelong disease-related symptoms. Eculizumab is not a curative treatment and patients are likely to receive life-long treatments for disease management in addition to IV infused eculizumab (e.g. blood transfusions) (para 6.74, ravulizumab PSD, July 2020 PBAC meeting). The ESC considered its previous concerns regarding the application of utility values in the model remain relevant to the resubmission.</p>	High, favours eculizumab

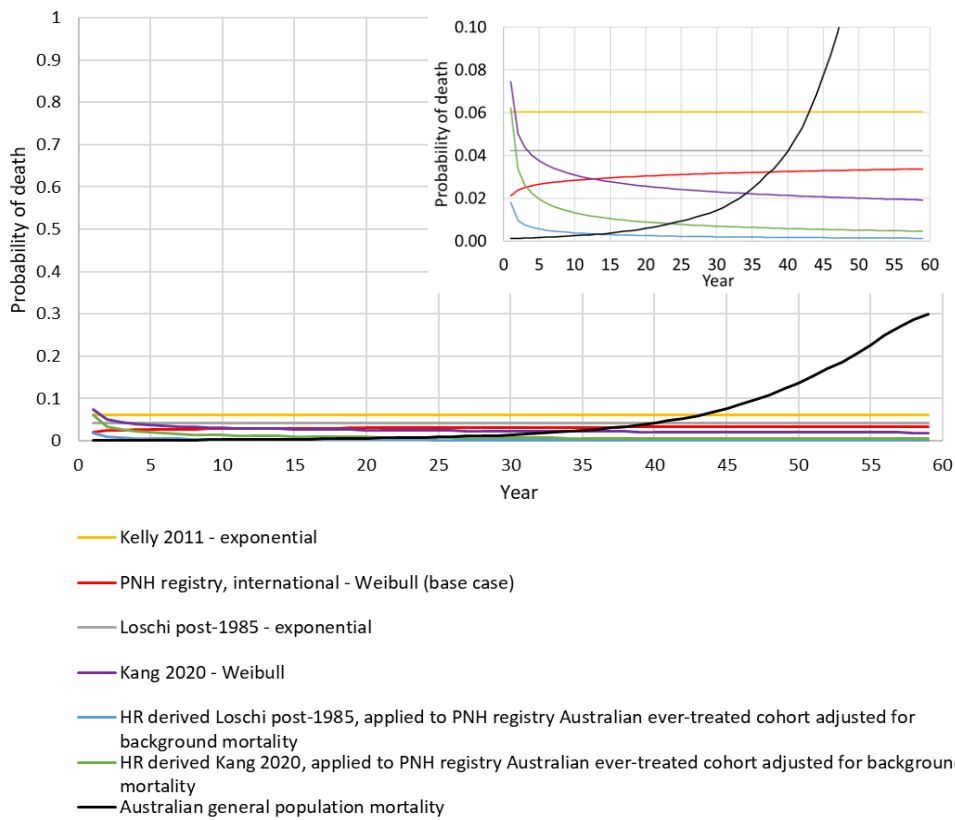
Source: constructed during the evaluation

Figure 2: Transition probabilities to death in the eculizumab arm



Source: Constructed during the evaluation using Ecu Rav CUA economic model Excel workbook provided with the resubmission

Figure 3: Transition probabilities to death in the BSC arm



Source: Constructed during the evaluation using Ecu Rav CUA economic model Excel workbook provided with the resubmission

Note: Inset graphs represents the transition probabilities with Y-axis scale between 0 and 0.1

- 6.80 In the base case, modelled hazards of death in the eculizumab arm declined over time and were less than general population mortality by Year 7. Modelled hazards of death in the BSC arm of the base case increased over time but were less than general population mortality by Year 37 in the model.
- 6.81 The modelled hazards for the base case and clinical inputs used in sensitivity analyses (Kelly 2011, Loschi 2016 post-1985 and Kang 2020) appeared clinically implausible. A mortality adjustment was required to ensure the modelled hazards meet face validity (i.e. were at least that of the general population). The ESC previously considered the requirement for a survival cap suggests the model is not capturing survival appropriately (para 6.73, ravulizumab PSD, July 2020 PBAC meeting).
- 6.82 The resubmission estimated eculizumab drug costs based on the ex-manufacturer price, without mark-ups or dispensing fees. The resubmission claimed that the use of ex-manufacturer pricing was appropriate as the majority of use would be in public hospitals (90%) and mark-ups for private hospital use would be negligible relative to the drug acquisition cost.
- 6.83 The resubmission assumed 100% adherence and persistence to eculizumab in the model. This was inconsistent with trial data suggesting some discontinuations during the 26-week trial period due to patient and physician decision, lack of efficacy and pregnancy. Utilisation data from the LSDP review of eculizumab suggests an average treatment duration of approximately [REDACTED] years including treatment breaks (LSDP review). The report also stated that [REDACTED] of the [REDACTED] patients (between 2011-2019) have stopped treatment, with [REDACTED] of the [REDACTED] known to be deceased. It was assumed that the remaining [REDACTED] patients are alive but not treated with eculizumab on the LSDP. However, the report noted gaps in the AIHW cause of death data linkage therefore it is possible that more patients are deceased (LSDP report). The reasons for treatment discontinuation were unknown due to limited documentation in the LSDP dataset, however, it is likely that a number of these patients left the LSDP to participate in clinical trials (estimated as < 500 patients from 2017 in the resubmission).
- 6.84 While there were concerns with the data source and/or derivation of a number of the other cost inputs, the incremental costs were primarily driven by eculizumab drug costs.
- 6.85 There were no costs or consequences attributed to the increased risk of serious infections and infusion reactions associated with eculizumab treatment. This approach was inconsistent with the clinical claim of inferior safety versus BSC.
- 6.86 The results of the modelled economic evaluation are summarised below.

Table 13: Results of the stepped economic evaluation

Step and component	Eculizumab	BSC	Increment
Step 1a: Overall survival based on Kaplan-Meier survival curves for eculizumab versus BSC (Australian ever treated versus international never treated) from adjusted-with LDH PNH registry analysis), 6-year time horizon, drug and administration costs only^a			
Costs	\$ [redacted]	\$0	\$ [redacted]
LYs	5.92	5.58	0.34
Incremental cost/LY gained			\$ [redacted] ¹
Step 1b: Modelled efficacy (log-normal survival curve for eculizumab; Weibull survival curve for BSC), 6-year time horizon, drug and administration costs only^a			
Costs	\$ [redacted]	\$0	\$ [redacted]
LYs	5.93	5.59	0.34
Incremental cost/LY gained			\$ [redacted] ¹
Step 2: Extrapolate to 60-year time horizon^a			
Costs	\$ [redacted]	\$0	\$ [redacted]
LYs	57.46	28.22	29.24
Incremental cost/LY gained			\$ [redacted] ²
Step 3: Incorporate age-adjusted survival cap (i.e. proportion remaining alive does not exceed general population survival estimates)^a			
Costs	\$ [redacted]	\$0	\$ [redacted]
LYs	41.53	26.47	15.06
Incremental cost/LY gained			\$ [redacted] ¹
Step 4: Include anticoagulation drug costs, blood transfusion costs, thromboembolic event costs, specialist visit costs and meningococcal vaccine costs^a			
Costs	\$ [redacted]	\$87,548	\$ [redacted]
LYs	41.53	26.47	15.06
Incremental cost/LY gained			\$ [redacted] ¹
Step 5: Include baseline utilities^a			
Costs	\$ [redacted]	\$87,548	\$ [redacted]
QALYs	31.40	20.01	11.39
Incremental cost/QALY gained			\$ [redacted] ¹
Step 6: Include disutility for thromboembolic events^a			
Costs	\$ [redacted]	\$87,548	\$ [redacted]
QALYs	31.37	19.90	11.47
Incremental cost/QALY gained			\$ [redacted] ¹
Step 7: Include non-specific disease-related utility gain (applied to eculizumab arm) and a non-specific disease-related disutility (applied to BSC arm)^a			
Costs	\$ [redacted]	\$87,548	\$ [redacted]
QALYs	35.18	18.32	16.86
Incremental cost/QALY gained			\$ [redacted] ³
Step 8: Incorporate age-adjusted general population utility cap^a			
Costs	\$ [redacted]	\$87,548	\$ [redacted]
QALYs	35.00	18.32	16.69
Incremental cost/QALY gained			\$ [redacted] ³
Step 9: Apply 5% discount rate to costs and consequences			
Costs	\$ [redacted]	\$42,154	\$ [redacted]
QALYs	14.45	8.84	5.62
Incremental cost/QALY gained (base case)			\$ [redacted] ¹

Source: constructed during the evaluation using the 'Ecu Rav CUA economic model workbook' of the resubmission

Abbreviations: LY, life years; QALY, quality adjusted life years

^a Estimates were calculated during the evaluation

The redacted values correspond to the following ranges:

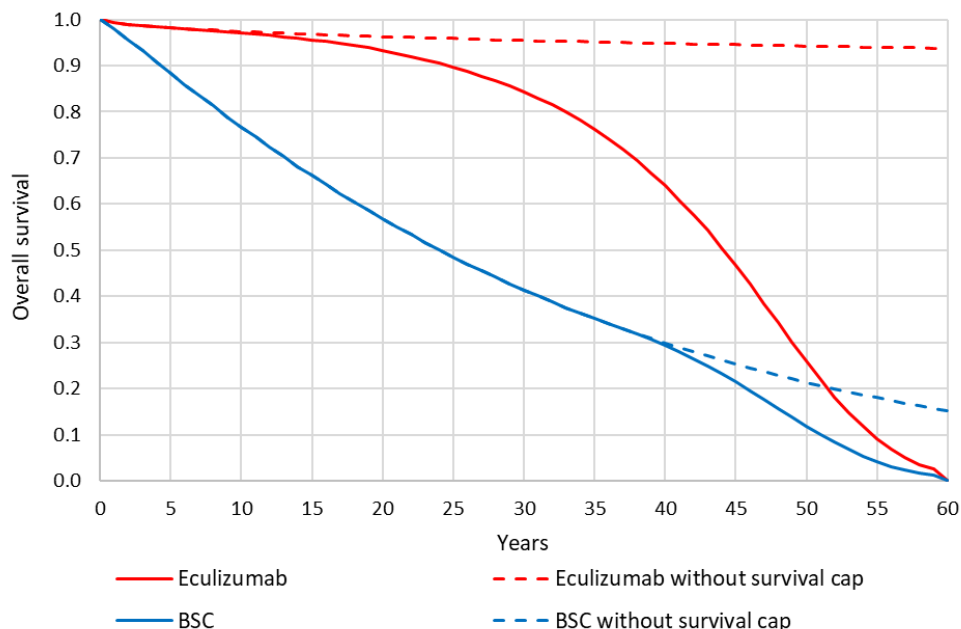
¹ > \$1,055,000

² \$755,000 to < \$855,000

³ \$955,000 to < \$1,055,000

- 6.87 The extrapolation to 60 years, incorporation of the age-adjusted survival cap, inclusion of non-specific disease-related utility differences and discounting had the largest impacts on the stepped economic evaluation.
- 6.88 Based on the economic model, treatment with eculizumab versus BSC in adult patients with PNH (who are eligible for treatment on the LSDP) was associated with a cost per QALY gained of > \$1,055,000. The cost-effectiveness estimate was uncertain due to concerns with the robustness and generalisability of the survival data, and extrapolation methods that generated clinically implausible survival estimates. These issues are unlikely to be resolved with the available data.
- 6.89 The figure below illustrates overall survival between treatment arms (with and without background mortality adjustment) over the model duration.

Figure 4: Overall survival in the base case of the economic model



Source: Constructed during the evaluation using Ecu Rav CUA economic model Excel workbook provided with the resubmission

- 6.90 The survival curves rapidly separate from the start of the model to approximately 30 years in the model, after which the curves begin to converge. Beyond 7 years in the model, patients in the eculizumab arm can only die due to age-adjusted mortality. In the BSC arm, patients are at an increased risk of mortality until 38 years, after which they can only die due to age-adjusted mortality. The ESC considered that it was clinically unreasonable to assume that people with PNH would have the same mortality as the general population after 7 years of treatment.
- 6.91 The resubmission did not present other validation or discussions regarding the face validity of modelled survival which required a survival cap based on age-adjusted general population mortality. The PSCR stated that survival capping was a necessary

step of survival extrapolation using parametric functions. The ESC considered this claim was inadequately justified as the face validity of survival estimates (as model outputs) should be considered when choosing input data and methods of extrapolation (i.e. choice of survival function) based on the nature of the disease and associated hazards of death. The ESC noted that based on Figure 4, even with the application of a survival cap, approximately 25 % of people with PNH who receive eculizumab are still alive at age 90 (model duration 50 years) and approximately 12 % in the BSC arm. The ESC considered these findings further indicated the model lacked face validity.

6.92 Sensitivity analyses for the eculizumab versus BSC comparison were conducted during the evaluation and presented in the table below.

Table 14: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	5.62	\$ [REDACTED] ¹
Baseline age (base case: 40 years)			
12 years	\$ [REDACTED]	6.89	\$ [REDACTED] ¹
32 years	\$ [REDACTED]	6.24	\$ [REDACTED] ¹
45 years (age at treatment enrolment, LSDP review)	\$ [REDACTED]	5.11	\$ [REDACTED] ¹
49 years (current age as of 2019, LSDP review)	\$ [REDACTED]	4.63	\$ [REDACTED] ¹
Time horizon (base case: 60 years)			
6 years	\$ [REDACTED]	0.92	\$ [REDACTED] ¹
10 years	\$ [REDACTED]	1.64	\$ [REDACTED] ¹
20 years	\$ [REDACTED]	3.33	\$ [REDACTED] ¹
40 years	\$ [REDACTED]	5.30	\$ [REDACTED] ¹
Survival cap (base case: age- and gender-adjusted Australian general population mortality)			
No survival cap	\$ [REDACTED]	6.93	\$ [REDACTED] ¹
Modelled survival with survival cap (base case eculizumab: PNH registry, Australian ever-treated; BSC: PNH registry, international never-treated)			
Eculizumab: PNH registry, international ever-treated; BSC: PNH registry, international never-treated	\$ [REDACTED]	4.83	\$ [REDACTED] ¹
Eculizumab: Kelly 2011; BSC: Kelly 2011	\$ [REDACTED]	7.82	\$ [REDACTED] ²
Eculizumab: PNH registry, Australian ever-treated; BSC: Loschi 2016 (post-1985 subgroup)	\$ [REDACTED]	6.98	\$ [REDACTED] ³
Eculizumab: PNH registry, Australian ever-treated; BSC: Kang 2020	\$ [REDACTED]	6.55	\$ [REDACTED] ³
Eculizumab: PNH registry, Australian ever-treated; BSC: HR derived using Loschi post-1985 (HR: 2.63)	\$ [REDACTED]	3.89	\$ [REDACTED] ¹
Eculizumab: PNH registry, Australian ever-treated; BSC: HR derived using Kang 2020 (HR: 9.09)	\$ [REDACTED]	6.52	\$ [REDACTED] ³
Non-specific disease-related utility change (base case ravulizumab: 0.093, BSC: -0.061 applied every year)			
No utility change in BSC arm	\$ [REDACTED]	4.87	\$ [REDACTED] ¹
No utility change in eculizumab arm	\$ [REDACTED]	4.10	\$ [REDACTED] ¹
No utility change in both arms	\$ [REDACTED]	3.35	\$ [REDACTED] ¹
BSC arm disutility only, applied in the first 2 years	\$ [REDACTED]	3.46	\$ [REDACTED] ¹
Eculizumab utility gain only, applied in the first 2 years	\$ [REDACTED]	3.52	\$ [REDACTED] ¹
Eculizumab: 0.208, BSC: -0.155 (McKenzie 2009 mapping algorithm)	\$ [REDACTED]	7.48	\$ [REDACTED] ⁴

Source: constructed during the evaluation using the 'Ecu Rav CUA economic model workbook' of the resubmission

Abbreviations: EQ-5D-3L, EuroQol 5-dimension 3-level quality of life questionnaire; EQ-5D-5L, EuroQol 5-dimension 5-level quality of life questionnaire

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$755,000 to < \$855,000

³ \$955,000 to < \$1,055,000

⁴ \$855,000 to < \$955,000

- 6.93 The results were most sensitive to time horizon, non-specific disease-related utility changes and modelled survival data.
- 6.94 Changing the parametric survival function for extrapolation (with or without the survival cap) in the base case had relatively minimal impact on the ICER. This is because the predicted hazards of death for the eculizumab arm is informed by general population mortality for the majority of the modelled duration.
- 6.95 The resubmission included an exploratory analysis using a baseline age of 12 years to represent the cost-effectiveness of eculizumab versus BSC in the paediatric population. The analysis assumed that the treatment effect of eculizumab and all other inputs used for the adult population were generalisable to the paediatric population. No data were provided in support of this assumption.
- 6.96 During the evaluation, threshold analyses were conducted to determine the price reduction required for eculizumab to be cost-effective. At high thresholds of \$100,000, \$200,000 and \$300,000 per life year gained and QALY gained, price reductions required would be ■■■%, ■■■% and ■■■% for ICER per life year gained, and ■■■%, ■■■% and ■■■% for ICER per QALY gained. The PBAC noted these threshold analyses were not based on a robust model.

Cost-utility analysis of ravulizumab versus best supportive care

- 6.97 The model structure and inputs for the ravulizumab versus BSC comparison were largely the same as for the eculizumab versus BSC comparison, except for a relatively small difference in treatment costs. As outlined in paragraph 6.74, the ESC considered the model structure lacked face validity and was unlikely to be reliable for decision making.
- 6.98 Ravulizumab drug costs were estimated assuming no wastage with use of the requested formulations of the higher strength ravulizumab based on the most efficient vial combinations for each weight band (40 to <60 kg, 60 to <100 kg and 100 kg or more). It was unclear how the most efficient vial combination would be obtained under the Section 100 Highly Specialised Drugs Program. There is potential for wastage should prescribers request vial combinations other than proposed in the resubmission.
- 6.99 The resubmission assumed 100% treatment adherence and persistence. No justification was provided for this assumption, which was inconsistent with trial discontinuation data and utilisation data provided in the LSDP report.
- 6.100 The total drug and administration cost for ravulizumab in the initial year (\$■■■■) was higher compared to eculizumab (\$■■■■) despite a lower total dose for

ravulizumab (23,241 mg) compared to eculizumab (24,000 mg). The increased cost was primarily due to the higher cost per mg for ravulizumab (\$ [redacted]) versus eculizumab (\$ [redacted]) based on the cost-minimisation analysis. Treatment costs for ravulizumab (\$ [redacted]) and eculizumab (\$ [redacted]) were similar in subsequent years.

6.101 The results of the economic evaluation are presented in the table below.

Table 15: Results of the economic evaluation

Component	Ravulizumab	BSC	Increment
Costs	\$ [redacted]	\$42,154	\$ [redacted]
QALYs	14.45	8.84	5.62
Incremental cost/QALY gained			\$ [redacted] ¹
July 2020 consideration			
Incremental cost per QALY gained (revised base case)			\$ [redacted] ²

Source: Table 3.34, p272 and Table 3.37, p275 of the resubmission

Abbreviation: QALY, quality-adjusted life year

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$655,000 to < \$755,000

6.102 In the model, 69.9% of the incremental costs; 93.7% of the incremental life years; 83.6% of the incremental QALYs are accrued in the extrapolated period (beyond 6 years).

6.103 Based on the economic model, treatment with ravulizumab versus BSC in adult patients with PNH (who are eligible for treatment on the LSDP) was associated with a cost per QALY gained of > \$1,055,000. The results were similar to the comparison of eculizumab versus BSC (cost per QALY gained of > \$1,055,000), with a small difference primarily due to higher treatment costs in the initial year. The cost per QALY gained was higher compared to the July 2020 ravulizumab submission, primarily due to changes to the survival data and extrapolation and removal of transitions to spontaneous remission.

Drug cost/patient/year

6.104 The estimated drug cost for eculizumab per patient per year, based on the proposed effective AEMP of \$ [redacted] per 300 mg vial, was \$ [redacted] in the initial year (80 vials for loading and maintenance doses) and \$ [redacted] in subsequent years (78 vials for maintenance doses only).

6.105 The estimated drug cost for ravulizumab per patient per initial year and subsequent years was calculated based on the proposed effective AEMP of \$ [redacted] per 300 mg vial and \$ [redacted] per 1,100 mg vial for all weight bands, summarised in the table below.

Table 16: Ravulizumab drug cost per patient per year

Body weight	Initiation year (Loading dose plus 6.25 maintenance doses)		Drug cost/ patient/year	Maintenance year (6.5 maintenance doses)		Drug cost/ patient/year
	300 mg vial	1,100 mg vial		300 mg vial	1,100 mg vial	
≥ 40 to < 60 kg	70.5	0	\$ [REDACTED]	65.0	0	\$ [REDACTED]
≥ 60 to < 100 kg	9	18.75	\$ [REDACTED]	0	19.5	\$ [REDACTED]
≥ 100 kg	16.25	18.75	\$ [REDACTED]	6.5	19.5	\$ [REDACTED]

Source: Section 4 BIM Excel workbook of the resubmission

6.106 The estimated drug cost per patient per year for ravulizumab used in the economic evaluation and financial estimates was calculated in the resubmission assuming no wastage based on the most efficient vial combination. It was unclear how the most efficient vial combination would be obtained under the Section 100 Highly Specialised Drugs Program. There is potential for wastage should prescribers request vial combinations other than proposed in the resubmission.

Estimated PBS usage & financial implications

6.107 Compared to the July 2020 submission, the main changes to the estimated use and financial implications were:

- Revised eligible population estimates based on a market share approach rather than an epidemiological approach. The grandfathered population was merged into the prevalent population.
- Revised ravulizumab pricing based on a cost-minimisation analysis (which included the April 2021 price reduction for eculizumab) rather than a cost-effectiveness analysis.
- The inclusion of two vial sizes, 300 mg and 1,100 mg (both formulations also based on a higher concentration per vial of 100 mg/mL).
- The exclusion of cost-offsets for previous LSDP patients returning from clinical trials.
- Revised number of scripts per patient based on the number of administrations rather than the number of vials. A patient co-payment was introduced for each script.
- The inclusion of new/modified Special Pricing Arrangements and Risk Sharing Arrangements.

6.108 While the resubmission acknowledged the potential for both eculizumab and ravulizumab to be considered for PBS listing, the resubmission did not provide financial estimates for the costs associated with transferring eculizumab from the LSDP to the PBS.

6.109 DUSC did not consider this resubmission. The resubmission used a market share approach to estimate the utilisation and financial impact of ravulizumab. Key inputs are summarised in the table below.

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Patients eligible for C5 inhibitors	Eligible population increasing from █ ¹ patients in Year 1 to █ ¹ patients Year 6 in 2027. Based on the sponsor's eculizumab LSDP order data (2015-2021) with an adjustment for an additional █ ¹ known patients in the sponsor's clinical trials and an estimated █ ¹ patients in competitor clinical trials. Population estimates were extrapolated using a linear function	<p>Market share estimates were based on proprietary data that could not be validated during the evaluation. There were discrepancies in the number of patients treated with eculizumab on the LSDP that was estimated in the resubmission versus estimates provided by the LSDP Secretariat. The reasons for these discrepancies were unknown but could be due to timing (calendar year versus financial year) or data source (order data could differ from actual patient numbers due to treatment breaks or non-compliance).</p> <p>The resubmission estimated a change in the annual net growth of the C5 inhibitor population from █ per year (based on Deed of Agreement LSDP projections) to █ per year but did not provide sufficient historical data to explain the change in growth projections.</p> <p>While the adjustment for patients in clinical trials increased the number of patients eligible for C5 inhibitors, the resubmission assumed negligible population growth between 2017-2018 (net change: 0 patients) and 2019-2020 (net change: -1 patient). These plateaus do not appear consistent with the underlying epidemiology of the disease which would suggest a gradual increase over time.</p>
Ravulizumab uptake rate	Assumption of █% uptake based on reported patient preference for ravulizumab vs. eculizumab in the PNH-302 sub-study with acknowledgement that some patients are not suitable for ravulizumab treatment (i.e. children, pregnant women)	<p>The estimated uptake rate of ravulizumab is difficult to quantify but is likely to be high given the reduced treatment burden compared to eculizumab.</p> <p>Patient preference rates were based on patients who had trialed both medicines and may not be representative of patients successfully managed with eculizumab.</p> <p>The generalisability of trial-based estimates to clinical practice was unclear.</p>
Estimated ravulizumab vials per patient	Average loading dose: 8.96 x 300 mg vials; average vials per year for treatment initiation or switch: 17.98 x 300 mg and 16.23 x 1100 mg vials; average vials per year for prevalent patients: 9.38 x 300 mg and 16.88 x 1100 mg vials. Based on product information and using reported weight distribution from the Australian PNH registry	<p>The PNH registry represents a subset of the target population and it is unclear whether the demographics of the registry are generalisable to the broader population.</p> <p>The resubmission has assumed that the most efficient combination of vials will be used and therefore there would be no wastage in clinical practice. It was unclear whether this assumption was reasonable.</p> <p>The resubmission has assumed perfect compliance to treatment which is unlikely to reflect clinical practice</p>
Cost of ravulizumab vials	Weighted effective DPMQ based on 10.44% private (300 mg: \$█; 1100 mg: \$█) and 89.56% public (300 mg: \$█; 1,100 mg: \$█) hospital use. The weighting was based on eculizumab use on the PBS in 2020 for the treatment of atypical haemolytic uraemic syndrome	<p>The resubmission inappropriately applied fees and markups (included in the proposed DPMQ) to each vial dispensed rather than each script dispensed.</p>
Average eculizumab vials	Incident population: 80 vials per year; prevalent population: 78 vials per year. Based on recommended	<p>The resubmission assumed perfect compliance to treatment which is unlikely to reflect clinical practice.</p>

Public Summary Document – July 2021 PBAC Meeting

Parameter	Value applied and source	Comment
per substituted patient per year	dosing regimen in product information	
Cost per eculizumab vial	\$█. Effective vial price under the current LSDP Deed of Agreement	This was reasonable.
Number of infusions per patient per year	Ravulizumab: 7.25 (incident/switch) or 6.50 (prevalent). Eculizumab: 28 (incident) or 26 (prevalent). Based on recommended dosing regimen in product information	The resubmission has assumed perfect compliance to treatment which is unlikely to reflect clinical practice.
Cost of infusion	\$111.40. 85% of Scheduled fee for MBS 13950 (parenteral administration of an antineoplastic agent)	The resubmission did not adequately justify the use of an MBS item for chemotherapy medicines. The Manual of Resource Items v5.0 recommends the use of a standard MBS consultation item if there is no specific MBS item for the administration of the proposed drug. MBS item 105 for a follow-up specialist visit attracts a Schedule fee of \$45.00.

Source: Table 4.1, p 281, Table 4.2, p281-283 of the resubmission

The redacted values correspond to the following ranges:

¹ < 500

6.110 The table below presents the estimated use and financial implications of ravulizumab over 6 years of listing.

Table 18: Estimated use and financial implications

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Extent of use						
Patients eligible for C5 inhibitors	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Ravulizumab uptake rate (■%)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Financial implications						
Total cost for ravulizumab 300 mg and 1100 mg dose strengths (effective)	\$■ ²	\$■ ²	\$■ ²	\$■ ²	\$■ ³	\$■ ³
■ (cost of 8.96 x 300 mg vials per patient switching from eculizumab)	-\$■ ⁴	-	-	-	-	-
Patient co-payment (\$29.42 per script)	-\$■ ⁴	-\$■ ⁴	-\$■ ⁴	-\$■ ⁴	-\$■ ⁴	-\$■ ⁴
Net cost to the PBS	\$■ ⁵	\$■ ²	\$■ ²	\$■ ²	\$■ ³	\$■ ³
LSDP costs of substituted eculizumab treatment	-\$■ ⁵	-\$■ ⁵	-\$■ ⁵	-\$■ ²	-\$■ ²	-\$■ ²
Change in treatment administration costs	-\$■ ⁴	-\$■ ⁴	-\$■ ⁴	-\$■ ⁴	-\$■ ⁴	-\$■ ⁴
Net cost to government	\$■ ⁴	\$■ ⁴	\$■ ⁴	\$■ ⁴	\$■ ⁴	\$■ ⁴
Net cost to the PBS (July 2020)	\$■ ⁵	\$■ ²	\$■ ³	\$■ ⁶	\$■ ⁶	\$■ ⁷
Net cost to government (July 2020)	\$■ ⁴	\$■ ⁴	\$■ ⁴	\$■ ⁴	\$■ ⁴	\$■ ⁴

Source: Table 4.9, p289-290; Table 4.10, p290-291; Table 4.12, p291; Table 4.13, p293; Table 4.16, p295-296; Table 4.17, p297; Table 4.19, p298; Table 4.20, p299; Table 4.22, p300; Table 4.23, p301; Table 4.24, p301-302 of the resubmission

^a The apparent difference in Year 1 incident estimates compared to subsequent years was due to rounding as actual estimates from prior years were based on whole numbers while predicted estimates used decimal places

The redacted values correspond to the following ranges:

¹ < 500

² \$50 million to < \$60 million

³ \$60 million to < \$70 million

⁴ \$0 to < \$10 million

⁵ \$40 million to < \$50 million

⁶ \$70 million to < \$80 million

⁷ \$80 million to < \$90 million

6.111 The net cost of listing ravulizumab on the PBS was estimated to be up to \$60 million to < \$70 million in the sixth year of listing, with a cumulative total cost of \$300 million to < \$400 million over six years. The resubmission also estimated savings of \$200 million to < \$300 million over six years to the LSDP due to substitution and a saving of \$0 to < \$10 million over six years to the MBS due to reduced administration costs. The net cost to government was \$40 million to < \$50 million over six years which was primarily due to market growth associated with patients switching to subsidised ravulizumab treatment after previously being enrolled in clinical trials, with no cost offsets assumed for these patients. The PBAC agreed with the ESC that patients may continue to be enrolled in clinical trials going forward and this market growth was not justified.

- 6.112 The previous July 2020 submission estimated that listing ravulizumab would be associated with a cumulative net cost of \$400 million to < \$500 million over six years to the PBS. The ESC noted that the difference in PBS financial implications was primarily due to a reduction in the estimated population size (due to the switch from an epidemiological to a market share approach) and reduction in ravulizumab price (cost-minimised price compared to eculizumab).
- 6.113 The previous July 2020 submission estimated that listing ravulizumab would be associated with a cumulative net cost to the government including offsets due to substitution of eculizumab (LSDP drug acquisition and treatment administration costs) of \$40 million to < \$50 million over six years. While appearing similar to current estimates, the previous estimates were based on a higher proposed price for ravulizumab but included a larger cost-offset associated with the substitution of eculizumab use on the LSDP.

Quality Use of Medicines

- 6.114 The resubmission stated the sponsor's intent to conduct quality use of medicines activities to support the listing of ravulizumab for the treatment of paroxysmal nocturnal haemoglobinuria.
- 6.115 The resubmission argued that there would be no wastage should the most efficient vial combinations be used for each weight band. However, the prescribing of drugs listed under the requested Section 100 – Highly Specialised Drugs Program is not limited to the most efficient combination. The availability of a larger vial size increases the potential for wastage and also introduces administrative burden (e.g. patients within the 100 kg or more weight band would require 2 prescriptions of differing quantities to achieve the most efficient combination). The availability of two vial sizes also increases the risk of medication error, particularly given combinations of both vials are required to prevent wastage. The PSCR disagreed that the availability of two vials would increase the risk of medication error, noting that the 3 mL and the 11 mL vials differ only in volume not concentration and are differentiated by colour branding. The PSCR instead argued that the increased drug concentrations allow for use of significantly fewer vials and reduced infusion times.

Financial Management – Risk Sharing Arrangements

- 6.116 The resubmission proposed a new Special Pricing Arrangement consisting of a [REDACTED] % rebate on the published DPMQ per script.
- 6.117 The resubmission proposed a revised Risk Sharing Arrangement to manage uncertainty in costs to government should ravulizumab be listed on the PBS. The proposal is based on two linked components; [REDACTED] and [REDACTED] [REDACTED] in patients previously treated with eculizumab.
- 6.118 The resubmission proposed revised [REDACTED] based on the [REDACTED] [REDACTED] over 6 years (summarised in the table below). The resubmission stated that these estimates are consistent with the estimated use of

eculizumab and ravulizumab in the budget impact model. As noted above, the expenditure growth was not justified.

Table 19: Commonwealth Payment Thresholds for New Deed

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Cost of ravulizumab	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ³	\$ [redacted] ³
Cost of eculizumab	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴
Commonwealth Payment Threshold (ex GST)	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ⁵
Estimated patient number	[redacted] ⁶	[redacted] ⁶	[redacted] ⁶	[redacted] ⁶	[redacted] ⁶	[redacted] ⁶

Source: Table 4.28, p305 of the resubmission

The redacted values correspond to the following ranges:

¹ \$40 million to < \$50 million

² \$50 million to < \$60 million

³ \$60 million to < \$70 million

⁴ \$0 to < \$10 million

⁵ \$70 million to < \$80 million

⁶ < 500

6.119 The resubmission noted that the proposed [redacted] for C5 inhibitors does not include the cost of [redacted].
 Alternatively, if the preference for the government is for [redacted], then the sponsor is willing to monitor the [redacted].

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (written) listing of ravulizumab for the treatment of paroxysmal nocturnal haemoglobinuria (PNH), on the basis that it should be available only under special arrangements under the Section 100 – Highly Specialised Drugs Program. The PBAC considered the clinical evidence presented demonstrated that ravulizumab was likely to be non-inferior in safety and effectiveness compared to eculizumab. The PBAC noted that eculizumab is currently funded on the Life Saving Drugs Program (LSDP). The PBAC considered the submission for ravulizumab provided an opportunity to reassess the cost-effectiveness of eculizumab for listing on the PBS. The PBAC considered the clinical data presented supported a survival advantage for eculizumab over best supportive care (BSC). 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 at a reduced price. The PBAC advised ravulizumab be listed based on a cost-minimisation to eculizumab.
- 7.2 The PBAC recommended eculizumab be moved from the LSDP to an Authority Required (written) listing for PNH, on the basis that it should be available only under special arrangements under the Section 100 – Highly Specialised Drugs Program. The PBAC is satisfied that eculizumab provides, for some patients, a significant improvement in efficacy over BSC. The PBAC's recommendation for listing was based on, among other matters, its assessment as described above, that the eculizumab would be appropriate for inclusion on the PBS with a price reduction that is greater than █%.
- 7.3 The PBAC's recommendation for listing ravulizumab 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 at the reduced price outlined in paragraph 7.2.
- 7.4 The PBAC noted recommendations from the LSDP Expert Panel on the review of PNH (see paragraph 2.3). The PBAC noted that Term of Reference 5 (ToR 5) was to 'Assess the value for money of eculizumab under the current funding arrangements by evaluating the benefit of the drug's treatment outcomes and cost'. The PBAC noted the findings of the Expert Panel Recommendations in relation to ToR 5 (see paragraph 2.5). The PBAC advised the submission for ravulizumab provided an opportunity to reassess the cost-effectiveness of eculizumab for listing on the PBS.
- 7.5 The PBAC accepted the submission suggestion for a PBS listing for both eculizumab and ravulizumab consistent with the current LSDP eligibility for eculizumab for initiation and continuation. However, the PBAC considered a PBS listing for eculizumab should, if possible, address the difference in the maintenance dosing interval between the existing eculizumab eligibility criteria on the LSDP (every 14 days)

and the approved Product Information (every 14 days \pm 2 days).

- 7.6 The PBAC noted the input from the sponsor hearing along with that from individuals, healthcare professionals and organisations which described the clinical need for eculizumab and ravulizumab treatment and the potential for improved disease control and quality of life with the longer-acting ravulizumab.
- 7.7 The PBAC reaffirmed its July 2020 advice that eculizumab was the appropriate comparator for ravulizumab (para 7.2, ravulizumab PSD, July 2020 PBAC meeting). The PBAC recalled that BSC was included as a secondary comparator as there is currently no PBS-listed medicine for PNH (para 7.2, ravulizumab PSD, July 2020 PBAC meeting). The PBAC noted that all data comparing ravulizumab to BSC was indirect, via a comparison of eculizumab against BSC, or from using eculizumab vs BSC as a proxy. The PBAC considered it was appropriate to use BSC as a way to determine the cost-effectiveness of a PBS listing for eculizumab.
- 7.8 The PBAC recalled that in July 2020 it had considered the magnitude of any survival benefit of eculizumab versus BSC was unclear, given the lack of contemporary data for BSC survival outcomes (para 7.4, ravulizumab PSD, July 2020 PBAC meeting). The PBAC noted the resubmission presented a review of published eculizumab survival data that included studies considered in the July 2020 ravulizumab submission and in the LSDP review, as well as new studies identified through literature searches. The PBAC agreed with the ESC that despite the inclusion of newer evidence, the published data representing BSC remained difficult to interpret as it was sparse, variable and largely dated in terms of data collection. It was also noted that there was limited data on life-threatening event such as thromboembolism. The PBAC noted the resubmission also provided eculizumab survival data from an unpublished analysis based on data from the International PNH Registry. The PBAC acknowledged the concerns raised by ESC regarding the robustness and applicability of the registry data (see paragraph 6.39). However, the PBAC agreed with the submission that the data from the International PNH Registry was the best available evidence to establish the magnitude of survival benefit versus BSC in this rare condition. The PBAC considered the results from the International PNH Registry supported a survival advantage for eculizumab over BSC and that, while the magnitude of that advantage remained uncertain, the claim of superior efficacy remained appropriate.
- 7.9 The PBAC considered the resubmission claim of inferior safety of eculizumab compared to BSC remained appropriate.
- 7.10 The PBAC recalled that it had previously considered ravulizumab is likely to be non-inferior to eculizumab in the short term (para 7.1, ravulizumab PSD, July 2020 PBAC meeting). The PBAC also recalled concerns that it may not be reasonable to assume that the superior survival benefit previously accepted for eculizumab compared to BSC can be applied to ravulizumab compared to BSC, in the absence of any long-term survival data for ravulizumab (para 7.4, ravulizumab PSD, July 2020 PBAC meeting). The PBAC noted the additional 2-year data from the extension periods of the key trials

provided in the resubmission and considered these data support maintenance of treatment effect with ravulizumab. The PBAC considered these data supported the claim of non-inferior efficacy of ravulizumab to eculizumab. Acknowledging that ravulizumab is a modified eculizumab molecule, the PBAC considered while the claim that ravulizumab (based on eculizumab data) was superior to BSC was uncertain, due to the caveats associated with the interpretation of available data, it would be reasonable to assume the benefit of ravulizumab over BSC would be similar to the benefit of eculizumab over BSC.

- 7.11 The PBAC reiterated the resubmission's claim of non-inferior safety compared to eculizumab and inferior safety compared to BSC was appropriate (para 7.9, ravulizumab PSD, July 2020 PBAC meeting).
- 7.12 The PBAC recalled that the ravulizumab July 2020 submission presented a cost-utility analysis of ravulizumab versus BSC, with the modelled inputs for survival and quality of life derived using eculizumab data and noted this approach was also used in the resubmission. The PBAC noted the resubmission used the same economic model to represent the cost-effectiveness of a PBS listing for eculizumab or ravulizumab versus BSC.
- 7.13 The PBAC reviewed the changes made to the modelled economic evaluation (see paragraph 6.73). The PBAC noted that in contrast to the July 2020 submission the resubmission model used data from the International PNH Registry to establish the magnitude of survival benefit versus BSC. The PBAC considered this data source appropriate (see paragraph 7.6). However, the PBAC noted the extrapolation methods for both the base case and sensitivity analyses generated modelled hazards of death that were less than general population mortality over time. The PBAC considered extrapolated survival in both treatment arms appeared clinically implausible and noted a survival cap was required to ensure the estimates meet face validity. The PBAC noted the resubmission also applied a utility cap to the 'on-treatment' utility value (see Table 12) to ensure that the utility estimates in the model meet face validity, as estimates exceeded those of the general population over the modelled duration.
- 7.14 The PBAC noted that based on the economic model, treatment with eculizumab versus BSC in adult patients with PNH was associated with a cost per QALY gained of > \$1,055,000. The PBAC considered the cost-effectiveness ratio was very high and uncertain due to the concerns outlined in paragraph 7.13. The PBAC considered that a substantial improvement in the body of evidence relating to BSC was unlikely given PNH is a rare disease and the established place in therapy of complement inhibitors for its treatment. In addition, the PBAC noted the LSDP Expert Panel Recommendations regarding the value for money of eculizumab under the current LSDP funding arrangements (see paragraph 2.5). As such, the PBAC considered it was unlikely that a more robust model in PNH could be developed. The PBAC advised that eculizumab would be appropriate for inclusion on the PBS with a price reduction that is greater than ■■■% to address the uncertainty in the cost-effectiveness. The PBAC

advised that with listing on the PBS for PNH, eculizumab would be removed from the LSDP for this indication.

- 7.15 The PBAC noted the resubmission presented a cost-minimisation analysis of ravulizumab versus eculizumab with the therapies costed over a 52-week maintenance period using the LSDP price per vial for eculizumab. The PBAC advised the cost-minimisation analysis should be conducted using the eculizumab price established following the outcomes of its considerations stated in paragraph 7.14. The PBAC also advised the administration costs should not be based on chemotherapy infusions, but rather should be based on the standard specialist follow-up consultation MBS item 105. In addition, the PBAC advised the cost-minimisation analysis should be conducted over a two year period from initiation of treatment, for consistency with other drugs considered by the Committee 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) is equivalent to eculizumab 47,400 mg (54 infusions).
- 7.16 The PBAC noted the resubmission financial estimates were revised from those presented in the July 2020 ravulizumab submission with the main changes outlined in paragraph 6.110. The PBAC noted the estimates were based on the ravulizumab pricing based on a cost-minimisation analysis and would need to be recalculated to take into account the outcome of its considerations stated in paragraph 7.15. The cost of administration should also be revised to be consistent with advice in paragraph 7.15. The PBAC also noted the resubmission did not provide budget impact estimates for the costs associated with transferring eculizumab from the LSDP to the PBS and that revision should be made to include the total eligible PNH population for PBS listing.
- 7.17 The PBAC considered a risk sharing arrangement 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.
- 7.18 The PBAC recommended that ravulizumab should be treated as interchangeable on an individual patient basis with eculizumab, according to s101(3BA) advice.
- 7.19 The PBAC advised that neither eculizumab nor ravulizumab are suitable for prescribing by nurse practitioners.
- 7.20 The PBAC recommended that the Early Supply Rule should not apply to either eculizumab or ravulizumab.
- 7.21 The requested restriction is considered to be complex.
- 7.22 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

Specifically the PBAC found that in the circumstances of its recommendation for eculizumab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies because the clinical data presented supported a survival advantage for eculizumab over BSC;

b) The treatment is not expected to address a high and urgent unmet clinical need because eculizumab is currently available on the LSDP;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.23 The PBAC noted that its recommendation for ravulizumab 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 2009 for Pricing Pathway A were not met.

7.24 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 Listing to be finalised.

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.