

An addendum to this public summary document has been included at the end of the document.

6.12 RAVULIZUMAB,

Solution concentrate for I.V. infusion 300 mg in 3 mL vial

Solution concentrate for I.V. infusion 1.1 g in 11 mL vial

Ultomiris[®],

Alexion Pharmaceuticals Australasia Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100 Authority Required listing for ravulizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS).
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus eculizumab.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description																																
Population	Patients with atypical haemolytic uraemic syndrome (aHUS)																																
Intervention	Ravulizumab: the recommended dosing regimen consists of a loading dose followed by maintenance dosing at a once every 8-week (≥ 20 kg) or 4-week (< 20 kg) interval, starting 2 weeks after loading dose administration. Doses are administered by intravenous infusion based on the patient's body weight, as shown below.																																
	<table border="1"> <thead> <tr> <th>Body weight range (kg)</th> <th>Loading dose (mg)</th> <th>Maintenance dose (mg)</th> <th>Dosing interval</th> </tr> </thead> <tbody> <tr> <td>≥ 5 to < 10</td> <td>600</td> <td>300</td> <td>Every 4 weeks</td> </tr> <tr> <td>≥ 10 to < 20</td> <td>600</td> <td>600</td> <td>Every 4 weeks</td> </tr> <tr> <td>≥ 20 to < 30</td> <td>900</td> <td>2100</td> <td>Every 8 weeks</td> </tr> <tr> <td>≥ 30 to < 40</td> <td>1200</td> <td>2700</td> <td>Every 8 weeks</td> </tr> <tr> <td>≥ 40 to < 60</td> <td>2400</td> <td>3000</td> <td>Every 8 weeks</td> </tr> <tr> <td>≥ 60 to < 100</td> <td>2700</td> <td>3300</td> <td>Every 8 weeks</td> </tr> <tr> <td>≥ 100</td> <td>3000</td> <td>3600</td> <td>Every 8 weeks</td> </tr> </tbody> </table>	Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)	Dosing interval	≥ 5 to < 10	600	300	Every 4 weeks	≥ 10 to < 20	600	600	Every 4 weeks	≥ 20 to < 30	900	2100	Every 8 weeks	≥ 30 to < 40	1200	2700	Every 8 weeks	≥ 40 to < 60	2400	3000	Every 8 weeks	≥ 60 to < 100	2700	3300	Every 8 weeks	≥ 100	3000	3600	Every 8 weeks
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For patients switching from eculizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, followed by maintenance doses starting 2 weeks after loading dose administration as per directions above.																																	
Comparator	Eculizumab: the recommended dosing regimen in patients ≥ 40 kg consists of an initial phase comprising 900 mg weekly intravenous infusions for 4 weeks followed by a maintenance phase of 1200 mg intravenous infusions every 2 weeks, starting in the fifth week. For patients < 40 kg, the initial and maintenance phase doses are weight-dependent, as outlined below.																																
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Complete TMA response (primary endpoint); time to complete TMA response; haematological normalisation (platelets, LDH); dialysis requirement status; change in CKD status; change in eGFR; quality of life (FACIT-Fatigue score and EQ-5D), safety																																	
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Outcomes	Complete TMA response (primary endpoint); time to complete TMA response; haematological normalisation (platelets, LDH); dialysis requirement status; change in CKD status; change in eGFR; quality of life (FACIT-Fatigue score and EQ-5D), safety																																
Clinical claim	Ravulizumab is noninferior in terms of efficacy and safety and has a reduced treatment burden relative to eculizumab.																																

Source: Table 1, p2 of the submission.

aHUS = atypical haemolytic uraemic syndrome; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy

2 Background

Registration status

2.1 Ravulizumab was TGA registered on 16 August 2022 for atypical haemolytic uraemic syndrome (aHUS). It is also registered for the treatment of paroxysmal nocturnal haemaglobinuria (PNH).

Previous PBAC consideration

2.2 Ravulizumab was listed on the PBS for the treatment of PNH following the PBAC recommendation in July 2021.

2.3 The history of the PBAC’s previous considerations of eculizumab for aHUS is summarised in Table 2. The DUSC had reviewed the use of eculizumab for aHUS 3 times and these reviews are included in the table.

Table 2: PBAC submission history – eculizumab for aHUS

Purpose	PBAC meeting date
aHUS; basis of current PBS restriction	March 2013 – not recommended due to uncertain clinical effectiveness and unacceptable cost effectiveness (Section 12, para 6, PSD March 2013)
	March 2014 – recommended with establishment of a managed entry scheme (Section 11, PSD, March 2014)
	August 2014 – out-of-session meeting to review criteria for managed entry scheme, including duration of treatment limited to 12 months (para 5.19, PSD, August 2014).
	December 2014 - listed without managed entry scheme or rebates
aHUS; to increase duration of treatment from 12 months to 24 months	December 2015 – recommended increasing duration from 12 to 24 months (para 3.14, PSD March 2018)
aHUS; patients with ESRD who are eligible for a renal transplant	March 2016 (minor) – not recommended on the basis of sparse data in support of use in a renal transplant setting (para 3.6, PSD, July 2017)
aHUS; patients with ESRD who are eligible for a renal transplant	July 2017 (minor) – recommended on the grounds that the PBAC was satisfied that prophylactic treatment with eculizumab reduced the risk of aHUS (para 7.5, PSD, July 2017), limited to 3 months treatment post-transplant (para 7.3, PSD, July 2017.)
DUSC review: 24 month predicted vs actual analysis of eculizumab use for aHUS (DUSC Abstract, Sep 2017)	Use of eculizumab for aHUS in terms of number of patients, vials and expenditure was more than double what was predicted in both the first and second years of listing. Since its listing in December 2014, 145 patients had been supplied eculizumab for aHUS at a cost to Government of \$71.5 million (to May 2017).
For the treatment of patients with aHUS in ESRD who are eligible for a renal transplant, to extend treatment duration	March 2018 (minor) - not recommended on the grounds that the evidence presented to support the longer duration of treatment [...] did not reliably address the key issues and did not prove substantial incremental benefit (para 7.1, PSD, March 2018).
DUSC review: utilisation update on Eculizumab for aHUS (DUSC Abstract, 2019)	Since its listing in December 2014, 220 patients had been supplied eculizumab for aHUS (to September 2018). Of 220, 82 were on treatment at the end of the analysis period (September 2018); 138 had stopped treatment and 12 had a break (of more than 84 days) followed by a second treatment episode. In 2017, 109 patients were supplied eculizumab, of whom 48 received their first PBS supply in 2017. The rate of growth in PBS patients has declined each year.
DUSC review: eculizumab for aHUS (DUSC Abstract, Oct 2020)	See text below for key findings.

Source: Table 7, p18 of the submission, with additional details added during evaluation.

aHUS = atypical haemolytic uraemic syndrome; ESRD = end stage renal disease; PSD = public summary document.

2.4 The key findings from the DUSC review in October 2020 were:

- Since its listing in December 2014, 323 patients have been supplied eculizumab for aHUS (to the end of May 2020). Of these 236 (73%) had stopped treatment and 87 (27%) were on treatment at the end of the analysis period.

- Of 298 patients supplied eculizumab from December 2014 to 20 March 2020, 74 had died. Of these 74, 39 (13.1% of total patient) died while on treatment. This suggests that some patients may have been treated despite disease progression.
- Adults (18 years and over) are 90.4% of patients treated with eculizumab.
- Of the top 3 prescriber types (general practitioners (GPs), nephrologists and haematologists), patients prescribed initial treatment by nephrologists and haematologists spent the longest amount of time on treatment.
- At the time of initial application approval, 68% of patients had an ADAMTS-13 score recorded and 32% did not. Of the patients without an ADAMTS-13 score at initial approval, 29.9% did not proceed to receive further treatment. The remaining 70.1% provided an ADAMTS-13 score and proceeded to receive the balance of initial supply.
- There were changes to the restriction in 2016, which may have led to a decrease in length of treatment. These changes included having to provide more information in the application: serial haematological results every 3 months while on treatment; evidence of an identifiable genetic mutation, if tested for, and prior history of aHUS.
- Restriction changes in January 2017 led to an increase in the number of adult patients. These changes included adding eligibility for treatment of organ damage, other than renal disease, caused by thrombotic microangiopathy (TMA), and clarification that the progressing TMA must be caused by aHUS.
- Initiating and prevalent patient numbers are showing signs of stabilising with 2019 being the first year that total patient numbers did not increase compared to the previous year.
- The rate of growth in the number of PBS patients supplied with eculizumab is declining.

2.5 A trend toward reduction in length of treatment, and stabilisation then reduction in the number of new patients, were also seen in data from the sponsor's global aHUS registry. ESC suggested that aHUS data from the Australian Thrombotic Microangiopathies (TMA) Registry (Monash University, School of Public Health and Preventive Medicine) may add local data around patient demographics, treatment initiation, treatment duration and reinitiating treatment. The PBAC welcomed the provision of demographic and treatment data from this independent registry, although acknowledged that it was a pragmatic registry with incomplete age and weight records and duration of treatment was unknown. The TMA Registry included 72 patients with aHUS, with a median follow-up time of 28 months and total follow-up of 1,940 patient months. The PBAC noted the higher proportion of paediatric patients compared to the 2020 DUSC review (26.4% of patient weighed less than 40 kg in the TMA registry compared to 9.6% from the 2020 DUSC review).

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Amount	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RAVULIZUMAB					
Ravulizumab 300 mg/3 mL injection, 3 mL vial	Private: \$6,621.94 Public: \$6,574.12 (published prices) Private: \$█ Public: \$█ (effective prices)	1	1	Initial (new patient): 0 Initial balance of supply: 2 Initial (switch patient) Extended continuing / recommencement: 3 Extended initial & continuing: 10	Ultomiris
Ravulizumab 1.1 g/11 mL injection, 11 mL vial	Private: \$24,152.93 Public: \$24,105.11 (published prices) Private: \$█ Public: \$█ (effective prices)	1	1	As above	Ultomiris

3.1 The submissions' requested restrictions are shown below. The submission used text in strikethrough to refer to changes and text in red to refer to additions compared to the corresponding PBS restriction for eculizumab. Treatment criteria and prescribing instructions are not shown as no changes to the PBS restrictions for eculizumab were requested.

Initial treatment (new patient) & Initial treatment – balance of supply

Category/Program: S100 Highly Specialised Drugs Program (Public/Private)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – written
Condition: Atypical haemolytic uraemic syndrome (aHUS)
Treatment phase: Initial treatment (new patient)
Clinical criteria
Patient must have active and progressing thrombotic microangiopathy (TMA) caused by aHUS,
AND
Patient must have ADAMTS-13 activity of greater than or equal to 10% on a blood sample taken prior to plasma exchange or infusion; or, if ADAMTS-13 activity was not collected prior to plasma exchange or infusion, patient must have platelet counts of greater than 30x10 ⁹ /L and a serum creatinine of greater than 150 mol/L,
AND
Patient must have a confirmed negative STEC (Shiga toxin-producing E.Coli) result if the patient has had diarrhoea in the preceding 14 days,
AND
Patient must have clinical features of active organ damage or impairment
AND
Patient must not receive more than 4 weeks 2 weeks of treatment under this restriction.
AND
The treatment must not be in combination with eculizumab.
Treatment phase: Initial treatment – balance of supply
Clinical criteria
Patient must have received PBS-subsidised initial supply of ravulizumab for this condition,
AND

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Patient must have ADAMTS-13 activity of greater than or equal to 10% on a blood sample,
AND
Patient must not receive more than 20 weeks 24 weeks supply under this restriction.
AND
The treatment must not be in combination with eculizumab.

Source: Table 16, p40 of the submission.

Initial treatment (switching from eculizumab)

Category/Program: S100 Highly Specialised Drugs Program (Public/Private)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – written
Condition: Atypical haemolytic uraemic syndrome (aHUS)
Treatment phase: Initial treatment (switching from eculizumab)
Clinical criteria
Patient must have received treatment under the initial restriction with PBS-subsidised eculizumab for this condition,
AND
Patient must have ADAMTS-13 activity of greater than or equal to 10% on a blood sample,
AND
Patient must not receive more than 32 weeks of treatment in total under this restriction including prior eculizumab use
AND
The treatment must not be in combination with eculizumab.
Administrative advice
Maximum quantities and repeats will only be authorised up to a total treatment duration of 32 weeks inclusive of duration of prior eculizumab for this treatment phase

Source: Table 17, p41 of the submission.

Extended initial treatment – Assessment phase / Continuing treatment and Extended Continuing treatment

Category/Program: S100 Highly Specialised Drugs Program (Public/Private)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – written
Condition: Atypical haemolytic uraemic syndrome (aHUS)
Treatment phase: Extended initial treatment – Assessment phase / Continuing treatment
Clinical criteria
Patient must have received treatment under the initial restriction with PBS-subsidised ravulizumab for this condition, OR Patient must have received treatment under either the 'Initial treatment', 'Extended initial treatment' or 'Continuing treatment' restriction with PBS-subsidised eculizumab for this condition,
AND
Patient must have demonstrated ongoing treatment response of PBS-subsidised ravulizumab or eculizumab treatment for this condition,
AND
Patient must not have experienced treatment failure with ravulizumab or eculizumab including PBS-subsidised ravulizumab or eculizumab for this condition,
AND
Patient must not receive more than 56 weeks [extended initial treatment] and 24 weeks [continuing treatment] 82 weeks of treatment in total under this restriction including prior eculizumab use
AND
The treatment must not be in combination with eculizumab.
Administrative Advice:
Maximum quantities and repeats will only be authorised up to a total treatment duration of 82 weeks inclusive of duration

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of prior eculizumab for this treatment phase
Treatment phase: Extended Continuing treatment
Clinical criteria
Patient must have received treatment under the Continuing treatment with PBS-subsidised ravulizumab or eculizumab for this condition,
AND
Patient must have demonstrated ongoing treatment response with PBS-subsidised ravulizumab or eculizumab for this condition,
AND
Patient must not have ever experienced treatment failure with ravulizumab or eculizumab including PBS-subsidised ravulizumab or eculizumab for this condition,
AND
Patient must have a TMA-related cardiomyopathy as evidenced by left ventricular ejection fraction < 40% on current objective measurement; OR Patient must have severe TMA-related neurological impairment; OR Patient must have severe TMA-related gastrointestinal impairment; OR Patient must have severe TMA-related pulmonary impairment on current objective measurement; OR Patient must have grade 4 or 5 chronic kidney disease (eGFR of less than 30 mL/min); OR Patient must have a high risk of aHUS recurrence in the short term in the absence of continued treatment with ravulizumab or eculizumab ,
AND
Patient must not receive more than 24 weeks 26 weeks of treatment per continuing treatment course authorised under this restriction including prior eculizumab use
AND
The treatment must not be in combination with eculizumab.
Administrative Advice
Maximum quantities and repeats will only be authorised up to a total treatment duration of 26 weeks inclusive of duration of prior eculizumab for this treatment phase.

Source: Table 18, p 42 of the submission.

Recommencement of treatment and Continuing recommencement of treatment

Category/Program: S100 Highly Specialised Drugs Program (Public/Private)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – written
Condition: Atypical haemolytic uraemic syndrome (aHUS)
Treatment phase: Recommencement of treatment
Clinical criteria
Patient must have demonstrated treatment response to previous treatment with PBS-subsidised ravulizumab or eculizumab for this condition,
AND
Patient must not have ever experienced treatment failure with ravulizumab or eculizumab including PBS-subsidised ravulizumab or eculizumab for this condition,
AND
Patient must have the following clinical conditions:(i) either significant haemolysis as measured by low/absent haptoglobin; or presence of schistocytes on the blood film; or lactate dehydrogenase (LDH) above normal; AND(ii) either platelet consumption as measured by either 25% decline from patient baseline or thrombocytopenia (platelet count <150 x 10 ⁹ /L);OR(iii) TMA-related organ impairment including on recent biopsy,
AND
Patient must not receive more than 24 weeks 26 weeks of treatment under this restriction including prior eculizumab use
AND

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The treatment must not be in combination with eculizumab.
Administrative Advice: Maximum quantities and repeats will only be authorised up to a total treatment duration of 26 weeks inclusive of duration of prior eculizumab for this treatment phase
Treatment phase: Continuing recommencement of treatment
Clinical criteria
Patient must have received treatment under Recommencement of treatment restriction with PBS-subsidised ravulizumab or eculizumab for this condition,
AND
Patient must have demonstrated ongoing treatment response to the previous 24 weeks of PBS-subsidised eculizumab or 26 weeks of PBS-subsidised ravulizumab for this condition,
AND
Patient must not have experienced treatment failure with ravulizumab or eculizumab including PBS-subsidised ravulizumab or eculizumab for this condition,
AND
Patient must not receive more than 24 weeks 26 weeks of treatment per continuing treatment course under this restriction including prior eculizumab use.
AND
The treatment must not be in combination with eculizumab.
Administrative Advice: Maximum quantities and repeats will only be authorised up to a total treatment duration of 26 weeks inclusive of duration of prior eculizumab for this treatment phase

Source: Table 19, p43 of the submission.

- 3.2 The submission proposed the following restrictions for ravulizumab: initial treatment; balance of supply for initial treatment; initial treatment for a patient switching from eculizumab; combining the ‘Extended initial treatment – Assessment’ and ‘Continuing’ phases, into a single phase; extended continuing treatment; recommencement and continuing recommencement treatment. The clinical and treatment criteria were similar to those for eculizumab, although proposed treatment durations differed.
- 3.3 The submission requested a ‘grandfathering restriction’ for patients currently receiving ravulizumab who would meet the PBS eligibility criteria upon listing as well as provisions for patients who are pregnant/breastfeeding and switch from ravulizumab to eculizumab (as is currently the case for the PBS listing of ravulizumab for the treatment of PNH). However, the submission did not provide proposed restriction wording for these settings.
- 3.4 For eculizumab, the current restrictions are for initial treatment, balance of supply of initial treatment, extended initial treatment – assessment phase, continuing treatment, extended continuing treatment, recommencement of treatment, and continuing recommencement of treatment.
- 3.5 Two key issues with respect to the listing and use of eculizumab have been the availability of ADAMTS-13 test results at the time of treatment initiation, and the duration of treatment. The current eculizumab and proposed ravulizumab durations of treatment are listed in Table 3.

Table 3: Current and proposed duration of treatment phases in the PBS restrictions

PBS treatment phase	Notes about treatment phase	Current eculizumab PBS listing	Proposed ravulizumab listing
		Duration of treatment per phase	
Initial treatment	Allows initiation pending ADAMTS-13 assay results	Maximum 4 weeks (4 x weekly doses)	Maximum 2 weeks (1 dose)
Initial treatment – balance of supply	ADAMTS-13 assay results required	Maximum 20 weeks (10 x 2-weekly doses). Total: 24 weeks including initial treatment	Maximum 24 weeks (3 x 8-weekly doses); Total: 26 weeks total including initial treatment; or Maximum combined total of 32 weeks if switching from eculizumab ^a
Extended initial treatment	Patients must demonstrate a response to access this treatment phase	Maximum 56 weeks	82 ^b weeks in total, including any eculizumab treatment (submission proposed merging extended initial and continuing treatment phases)
Continuing treatment		Maximum 24 weeks	
Total duration of first 4 phases		Maximum 104 weeks	Maximum 106 weeks (or maximum 116 weeks if switched from eculizumab)
Extended continuing treatment	Patients must be high risk to access this treatment phase which allows ongoing treatment.	24 weeks per script, on-going	26 weeks ^c
Recommencement of treatment	Allows recommencement in patients who previously discontinued a C5 inhibitor but experience a relapse while off treatment.	Maximum 24 weeks	26 weeks ^c
Continuing recommencement of treatment	Allows on-going access for above patients (i.e. who relapsed off treatment)	24 weeks per script, on-going	26 weeks ^c

Source: constructed during the evaluation based on Figure 6, p31 of the submission and the proposed restrictions presented in Table 16-19, pp40-43 of the submission.

^a The submission appeared to request 32 weeks in order to allow patients to switch prior to 24 weeks of eculizumab, then have a loading dose and one maintenance dose (i.e. 10 weeks) of ravulizumab therapy to stabilize and allow the logistics of obtaining authority approvals. The submission proposed a specific switching restriction for the 'Initial treatment – balance of supply' phase, but during subsequent phases proposed an additional 2 weeks of ravulizumab therapy to enable patients to switch at any point (i.e. to accommodate a loading dose during any phase).

^b i.e. 10 x 8-weekly doses plus allowance for one loading dose if required for patients switching from eculizumab during this treatment phase.

^c i.e. 3 x 8-weekly doses plus allowance for one loading dose if required for patients switching from eculizumab during this treatment phase.

3.6 In March 2018, the PBAC had recalled its December 2015 consideration of eculizumab, in which it recommended increasing the duration of treatment from 12 months to 24 months. It was noted in December 2015 that the evidence provided by the sponsor in 2014 showed that the vast majority of the benefit occurs in the first 6 months of eculizumab treatment, with some continuing improvement in the 6 to 12 month period. The 2-year follow-up data available in 2014 showed that there was no consistent improvement across all parameters in the 12 to 24 month period. Given that additional evidence was becoming available and had not been considered at the time the restrictions were specified, the PBAC recognised that the entry and continuation criteria warranted review. The 2015 PBAC recommendation that the

PBS-subsidy arrangements be extended for a further 12-months period, to 24-months was to enable this review to occur (paragraph 3.14, Eculizumab, Public Summary Document (PSD), March 2018).

- 3.7 To attempt to address this, the submission provided an overview of outcomes from the prospective registrational clinical studies of eculizumab; this is summarised in Table 6.
- 3.8 In the proposed restrictions for ravulizumab, the duration of initial treatment is shorter than the current duration for eculizumab. The submission stated that, '[r]esults from the ADAMTS-13 assay are typically available within 24 hours in current practice (particularly in public metropolitan centres; there may be delays in regional or private settings). While this result is also contingent on sampling taking place prior to administration of plasma therapy (otherwise measurement of ADAMTS-13 activity will be delayed by 1-2 weeks following the last plasma therapy), obtaining a plasma sample prior to onset of empiric therapy is now considered standard practice. Therefore, a 2-week initial treatment duration with ravulizumab, which corresponds to the duration of the single loading dose, prior to accessing balance of supply treatment is considered sufficient to attain an ADAMTS-13 result (compared with 4 weeks in the eculizumab restriction)'. The ESC advised that the ADAMTS-13 assay is desirable but not essential to diagnose aHUS. A low (0-5) PLASMIC score is also associated with a high probability of aHUS when administered to patients with a TMA and renal impairment. The pre-PBAC response stated that the PLASMIC scoring system has been shown to predict the likelihood of ADAMTS13 activity, and may be a useful tool for guiding treatment decisions while awaiting ADAMTS13 activity. However, it stated that current consensus is that the PLASMIC score '...cannot be used to definitively confirm or exclude the diagnosis of TTP' (George 2022). Moreover, it suggested that the PLASMIC scoring system is not currently routinely used in the diagnosis of aHUS in Australia.
- 3.9 The secretariat suggested that should ravulizumab be listed, the durations of initial treatment under each restriction should align with the shortest feasible duration. The Pre-Sub-Committee Response (PSCR) clarified the intent of the 2-week initial ravulizumab treatment phase (compared with 4 weeks currently in place for the eculizumab restriction) was to align with the loading dose duration of each respective treatment, as specified in the TGA-approved induction phases. Therefore, the PSCR considered it appropriate that the eculizumab restriction for initial treatment be maintained at 4 weeks.
- 3.10 The PBS does not subsidise drugs that are administered to admitted inpatients in a public hospital, with eculizumab being the only current exception. Given eculizumab is an anomaly, the following administrative note is required for the ravulizumab restriction to be consistent with PBS policy, 'This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.' The ESC advised that all new patients initiating C5 inhibitor therapy for treatment of aHUS would be expected to be inpatients in a public hospital, with patients transferred from regional centres as

required. The ESC expected that a substantial number of patients would remain admitted public hospital inpatients when commencing the initial treatment balance of supply restriction, administered at 2 weeks.

- 3.11 The pre-PBAC response acknowledged that eculizumab subsidy arrangements were an exceptional case and noted that the submission offered to [REDACTED]. The sponsor noted that it was open to working with the Department to achieve this intent.
- 3.12 The submission requested a Special Pricing Arrangement for the listing of ravulizumab for aHUS and a Risk Sharing Arrangement, with a combined expenditure cap for eculizumab and ravulizumab. The published price for aHUS was proposed to be the same as the published price for PNH.
- 3.13 The effective ex-manufacturer price for ravulizumab for PNH is currently \$ [REDACTED] for the 300 mg vial and \$ [REDACTED] for the 1100 mg vial. The effective prices proposed for aHUS were \$ [REDACTED] and \$ [REDACTED] respectively.

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

4 Population and disease

- 4.1 The submission stated that aHUS is an ultra-rare and life-threatening disease in which patients are continuously susceptible to unpredictable and progressive episodes of TMA due to uncontrolled activation of the alternative complement pathway. The condition affects both children and adults and can develop at any age. The submission cited a systematic review of epidemiological studies in aHUS (Yan 2020) that found prevalence estimates of aHUS ranging from 2.2 to 9.4 per million population among persons aged 20 years or younger, and 4.9 per million population for all age groups. Annual incidence estimates ranged from 0.26 to 0.75 per million population in those aged 20 years or younger, and from 0.23 to 1.9 per million population for all age groups.
- 4.2 Studies which included Australian/New Zealand cohorts reported an incidence of aHUS in paediatric patients of 0.44 per million annually and a prevalence of aHUS among adults of 2.4 per million, although each estimate was based on only one study.
- 4.3 The submission also stated that as there are no markers that distinguish aHUS from other causes of TMA, a treatment strategy for aHUS depends upon clinical presentation and a presumed diagnosis based upon exclusion of other causes of TMA. Evidence of a genetic abnormality is not required or recommended for diagnosis although genetic testing may ultimately confirm a diagnosis of aHUS and guide prognosis. One effect of this is that the number of patients who are treated for aHUS could rise or fall in the future, depending on the state of medical knowledge and clinical practice.
- 4.4 While DUSC reviews have found that changes made to the eculizumab restriction in 2016 may have led to decreases in the length of treatment (paragraph 2.4), future changes in the duration of treatment are difficult to predict. Patients without

pathogenic mutations in complement genes appear to have a lower risk of relapse when treatment is stopped, while those with mutations have a higher risk, although not all mutations have the same relapse risk. Greater understanding of pathogenic mutations in complement genes, and more widespread testing for mutations, may affect treatment duration. Because most of the pathogenic mutations associated with aHUS have a dominant pattern of inheritance, a family history of renal disease consistent with aHUS is an indication for continued treatment, and greater awareness of aHUS increases the likelihood that in the future a positive family history will be recognised.

- 4.5 The assumption of the submission is that most patients who are now on long-term treatment with eculizumab will switch to ravulizumab because of a preference for a greater dosing interval. This preference may also affect the choice between a trial of stopping treatment versus continued treatment at any given level of relapse risk.

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

5 Comparator

- 5.1 The submission nominated eculizumab as the comparator. The submission stated that ravulizumab has substituted 4 amino acids in the eculizumab heavy chain, resulting in a molecule targeting the same C5 epitope, but with a four-fold longer mean elimination half-life.
- 5.2 With respect to near market comparators, the submission noted that there may be biosimilars of eculizumab under development; it was not known whether they will be marketed in Australia. In addition, the submission stated that method of treatment patents for eculizumab do not expire until [REDACTED].
- 5.3 The recommended doses for ravulizumab and eculizumab are shown in detail in Table 1, as the dosage is key to the comparison of treatments.

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 clinicians outlined: the importance of rapid initiation of therapy; the significant impact of eculizumab treatment on survival outcomes compared with historically available agents and the biological plausibility of similar efficacy between eculizumab and ravulizumab. One clinician, with expertise using ravulizumab in the treatment of PNH, considered it unlikely that ravulizumab would be up-dosed in aHUS patients with borderline weight.
- 6.2 The PBAC asked follow-up questions regarding whether there had been any indication that there is breakthrough disease in patients with aHUS when treated with ravulizumab, particularly at weeks 6 – 8 prior to the next infusion, and what

percentage of patients were returning to use with eculizumab. The sponsor was not aware of any cases of breakthrough disease in practice, nor was any reported in the clinical studies 311 and 321. Based on real world experience from the UK there have been <500 out of <500 patients switched back to eculizumab in aHUS, all unrelated to breakthrough disease.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (14), health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described how ravulizumab and eculizumab were expected to provide similar levels of disease control, with known and manageable adverse events. It was suggested that patients should be allowed to switch treatments so long as they are responding to treatment. The comments particularly focused on the quality-of-life benefits associated with ravulizumab's increased treatment duration compared with eculizumab. By decreasing reliance on frequent hospital visits, ravulizumab treatment was expected to reduce missed days of school and work, improve finances, increase the ability to travel for longer periods of time. Having fewer infusions was also expected to improve access for other patients in hospital, and assist those patients with needle phobias and/or poor venous access.
- 6.4 The PBAC also noted input received from the Monash Medical Centre Transplant Unit, which emphasised the benefits of ravulizumab to patients in terms of decreasing reliance on hospital visits, particularly in the post-acute phase.
- 6.5 The PBAC also noted input received from aHUS alliance Global Action, including A report on the comparative experiences and expectations of the impact on aHUS patients following a transition from eculizumab to ravulizumab for the treatment of aHUS (a report based on 19 online interviews with patients and carers in the USA and UK undertaken in 2020). The organisation observed the following advantages with ravulizumab treatment:
- '75% reduction in infusions per year, saving time and any expense of attending treatments for patients and carers
 - less damage to patients' veins from fewer infusions and reduced anxiety from needling problems
 - opportunity to remove permanent lines and ports
 - less pre-infusion anxiety about potential delayed treatment
 - fewer infusion related side effect incidence e.g. headaches and tiredness
 - greater ability to travel between infusions particularly overseas for employment as well as leisure purposes
 - increased educational attainment and employment and career prospects due to less disruption from having to attend infusion treatment

- less time spent on home delivery and storage of equipment for home infusions
- ravulizumab offers a substantial treatment cost reduction.'

Clinical studies

- 6.6 The submission was based on 2 single arm studies of ravulizumab (studies 311 and 312) and 3 single arm studies of eculizumab (studies C08-002, C10-003, C10-004). No head-to-head trials were available. The submission provided published pooled analyses of the ravulizumab and eculizumab studies but did not use them. The comparative effectiveness was based on an unanchored adjusted indirect treatment comparison of the two drugs.
- 6.7 Details of the studies presented in the submission are provided in Table 4.

Table 4: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ravulizumab		
Study 311 NCT02949128	Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-naïve Adult and Adolescent Patients With Atypical Hemolytic Uremic Syndrome (aHUS) Rondeau, E., et al. The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. Barbour, T., et al. Long-Term Efficacy and Safety of the Long-Acting Complement C5 Inhibitor Ravulizumab for the Treatment of Atypical Hemolytic Uremic Syndrome in Adults. Gäckler, A., et al. Efficacy and safety of the long-acting C5 inhibitor ravulizumab in patients with atypical hemolytic uremic syndrome triggered by pregnancy: a subgroup analysis. Plus 6 abstracts based on the same study	February 2020 Kidney International 2020; 97(6): 1287-1296. Kidney International Reports 2021; 6(6): 1603-1613. BMC Nephrology 2021; 22(1).
Study 312 NCT03131219	A Phase 3, Open-label, Multicenter Study of ALXN1210 in Children and Adolescents With Atypical Hemolytic Uremic Syndrome (aHUS) Ariceta, G., et al. The long-acting C5 inhibitor, ravulizumab, is effective and safe in pediatric patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. Tanaka, K., et al. The long-acting C5 inhibitor, ravulizumab, is efficacious and safe in pediatric patients with atypical hemolytic uremic syndrome previously treated with eculizumab. Plus 3 conference abstracts based on the same study	NR Kidney International 2021;100(1): 225-237. Pediatric Nephrology 2021; 36(4): 889-898.
Study 311 and 312 (pooled analysis)	Dixon, B. P., et al. Two-year efficacy and safety of ravulizumab in adults and children with atypical hemolytic uremic syndrome (Ahus): Analysis of two phase 3 studies.	Blood 2021; 38(SUPPL 1): 769.
Eculizumab		
C08-002A/B NCT00844545/ NCT00844844	An open-label, multi-center controlled clinical trial of eculizumab in adult/adolescent patients with plasma therapy-resistant atypical Hemolytic-Uremic Syndrome (aHUS) 15 conference abstracts	Completed July 2015
C10-003 NCT01193348	An Open-Label, Multi-Center Clinical Trial of Eculizumab in Pediatric Patients with Atypical Hemolytic-Uremic Syndrome Greenbaum, L. A., et al. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. 7 conference abstracts	Completed April 2015 Kidney International 2016; 89(3): 701-711.
C10-004 NCT01194973	An Open-Label, Multi-Center Clinical Trial of Eculizumab in Adult Patients with Atypical Hemolytic-Uremic Syndrome. Fakhouri, F., et al. Terminal Complement Inhibitor Eculizumab in Adult Patients with Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial. 5 conference abstracts	Completed May 2017 American journal of kidney diseases 2016; 68(1): 84-93.
Indirect comparison ravulizumab vs eculizumab	Tomazos, I., et al. Comparative efficacy of ravulizumab and eculizumab in the treatment of atypical hemolytic uremic syndrome: An indirect comparison using clinical trial data.	Clinical Nephrology 2022; 97(5): 261-272.

Source: Table 26, pp 52-58 of the submission.

6.8 The key features of the included evidence are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Primary Outcome(s)
Ravulizumab studies					
Study 311	56	Single arm, OL, 26 wk, followed by extension until product registration or 4.5 years	High	≥12 years with aHUS and no previous eculizumab treatment	Platelet count ≥150 × 10 ⁹ /L and LDH ≤246 U/L), and ≥25% improvement in serum creatinine from baseline at 2 separate assessments obtained at least 28 days apart, and any measurement in between, at any time during initial 26 wk
Study 312	30	Single arm, OL, 26 wk, followed by extension until product registration or 4.5 years	High	<18 years with aHUS; previous eculizumab treatment permitted (10 patients)	Platelet count ≥150 × 10 ⁹ /L and LDH ≤246 U/L), and ≥25% improvement in serum creatinine from baseline at 2 separate assessments obtained at least 28 days apart, and any measurement in between, at any time during initial 26 wk
Eculizumab studies					
Study C10-004	41	Single arm, OL, 26 wk followed by extension until product registration or 2 years	High	≥18 years with aHUS	Platelet count ≥150 × 10 ⁹ /L and LDH ≤246 U/L), and ≥25% improvement in serum creatinine from baseline at 2 separate assessments obtained at least 28 days apart, and any measurement in between, at any time during initial 26 wk
Study C08-002	17	Single arm, OL, 26 wk followed by extension until product registration	High	>12 years and aHUS resistant to plasma exchange or infusion	Platelet count change from baseline including proportion of patients with platelets ≥150 × 10 ⁹ /L Secondary outcome: Platelet count ≥150 × 10 ⁹ /L and LDH ≤246 U/L for at least 2 consecutive measurements and for at least 4 weeks
Study C10-003	22	Single arm, OL, Single arm, OL, 26 wk followed by extension until product registration or 2 years	High	<18 years with aHUS	Platelet count ≥150 × 10 ⁹ /L and LDH ≤ 246 U/L), and ≥25% improvement in serum creatinine from baseline at 2 separate assessments obtained at least 28 days apart, and any measurement in between, at any time during initial 26 wk
Adjusted indirect treatment comparison					
Tomazos, I. et al.			High		Platelet count, LDH and change in serum creatinine at day 183 or if no day 183 data, closest date within 56 days before or after.

Source: Table 27, pp62-3 of the submission; Tomazos, 2022, p263.

OL = open label; aHUS = atypical haemolytic uraemic syndrome; LDH = lactate dehydrogenase

6.9 The studies were assessed using the Cochrane risk of bias assessment for single arm studies and were assessed in the submission as being at high risk for selection, performance, detection, and lead time bias. As stated in the submission, the process of patient recruitment was not clearly defined across the studies and could not be determined from review of the CSRs during the evaluation. In particular, although it is known how many patients of those screened were excluded (16/74 in Study 311 and 1/25 in Study 312) it is not known how many patients with aHUS were not screened, and, therefore, how selected a group the patients in the studies were. For example, Study 311 recruited 178 centres in 16 countries, but enrolled 58 patients at 41 centres

in 14 countries (311 CSR, p20/157). The global aHUS registry enrolled about 100 patients per year while the ravulizumab studies were recruiting, so there may have been a large number of patients with aHUS eligible for but not enrolled in the ravulizumab studies.

- 6.10 In the ravulizumab studies, treatment was for an initial 26-week period then up to 4.5 years or until the product was registered in the country of the study. In the eculizumab studies, treatment was continued after the initial 26-week treatment period until the product was registered or up to a maximum of 2 years. The median exposure periods are shown in Table 9. Although data for the number of infusions were provided, median dose was not provided.
- 6.11 Atypical haemolytic uraemic syndrome is a rare disease, and therefore randomised trials are relatively difficult to conduct. However, the sponsor's aHUS registry has enrolled 1,205 adult patients over 9 years, mainly in North America and the European Union. Between July 2019 and July 2021, 75 patients were enrolled who were treated with eculizumab. The evidence presented in the submission was a group of case series that have differences between the cohorts due to the change in practice following the introduction of eculizumab as well as the high risk of bias given the open label single arm design. Conclusions based on comparisons between the data sets are likely to be uncertain.

Global aHUS registry

- 6.12 The submission provided some data from an Alexion-sponsored registry of aHUS patients, most but not all treated with eculizumab, to address PBAC's previous concerns about the length of treatment. Table 6 shows data from this global aHUS registry compared to a DUSC analysis of eculizumab-treated patients, including additional data that was provided with the pre-PBAC response. This data has not been evaluated.
- 6.13 The global aHUS registry operates under protocol M11-001. The protocol was amended on 16 January 2020 to include ravulizumab-treated patients, including those participating in 'sponsored clinical studies'. Up to 11 April 2022, 41 ravulizumab-treated patients were enrolled. Of these, 37 (90.2%) had switched from eculizumab.

Table 6: Eculizumab-treated patients in the global registry and in data presented to DUSC to 2020/21.**

	Adult patients in M11-001 aHUS registry N = 808 ^a	Adult patients in M11-001 aHUS registry N = 850 ^b	Adult Australian patients in M11-001 aHUS registry N = 78 ^b	Adult East Asian ^d patients in M11-001 aHUS registry N = 22 ^b	DUSC data N = 323 ^e
Age at enrolment, years Mean (SD) Median (IQR)	42.0 (15.1) 39.4 (30.1, 52.6)	42.21 (15.052) 39.57 (30.31, 53.08)	45.04 (17.112) 40.34 (31.29, 57.04)	43.39 (16.673) 37.79 (30.31, 58.41)	NR
Female, n (%)	524 (64.9%)	552 (64.9)	50 (64.1)	13 (59.1)	NR
Year of first treatment ^f , n (%)					
2012		81 (9.5)	5 (6.4)	0 (0.0)	
2013		118 (13.9)	3 (3.8)	0 (0.0)	-
2014		113 (13.3)	10 (12.8)	0 (0.0)	-
2015		149 (17.5)	18 (23.1)	0 (0.0)	28 (8.7)
2016		144 (16.9)	16 (20.5)	3 (13.6)	48 (14.9)
2017		74 (8.7)	7 (9.0)	6 (27.3)	48 (14.9)
2018		29 (3.4)	3 (3.8)	2 (9.1)	47 (14.6)
2019		25 (2.9)	0 (0.0)	2 (9.1)	64 (19.8)
2020		22 (2.6)	3 (3.8)	6 (27.3)	56 (17.3)
2021		21 (2.5)	9 (11.5)	2 (9.1)	32 (9.9)
2022		9 (1.1)	2 (2.6)	1 (4.5)	
Year of registry enrolment ^f , n (%)					
2012	19 (2.4)				
2013	131 (16.2)				
2014	108 (13.4)				
2015	158 (19.6)				
2016	172 (21.3)				
2017	134 (16.6)				
2018	11 (1.4)				
2019	36 (4.5)				
2020	32 (4.0)				
2021	7 (0.9)				
2022					
Family history of aHUS, n (%)	86 (10.8%)	89 (10.5%)	9 (11.5%)	1 (4.5)	NR
Median duration of follow-up, years (range)	3.63 (0, 9)	3.91 (IQR: 1.83, 5.90)	2.90 (IQR: 0.50, 6.29)	2.03 (1.03, 4.43)	NR
Total time on treatment, years ^c Mean (SD) Median (IQR)	3.37 (2.76) 2.78 (1.01, 5.32)	3.58 (3.008) 2.87 (1.01, 5.61)	2.51 (2.658) 1.40 (0.47, 3.67)	2.63 (1.828) 1.99 (1.03, 4.55)	1.15 (NR) 0.42* (NR)
Deaths, n (%)	76 (9.4%)	84 (9.9%)	12 (15.4%)	5 (22.7%)	74/298 (24.8%)
Any discontinuation of eculizumab, n (%)	342 (42.3%) ^c	372 (43.8%)	46 (59.0%)	7 (31.8%)	236/323 (73.1%)
Any re-start of eculizumab after discontinuation, n (%)	57/342 (16.7%)	59/372 (15.9%)	10/46 (21.7%)	0 (0.0%)	NR
Reason for discontinuation, n (%)					
Lack of renal function improvement	65/342 (19.0%)	69/372 (18.5%)	2/46 (4.3%)	1/7 (14.3%)	NR

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	Adult patients in M11-001 aHUS registry N = 808 ^a	Adult patients in M11-001 aHUS registry N = 850 ^b	Adult Australian patients in M11-001 aHUS registry N = 78 ^b	Adult East Asian ^d patients in M11-001 aHUS registry N = 22 ^b	DUSC data N = 323 ^e
Lack of haematological improvement	18/342 (5.3%)	21/372 (5.6%)	3/46 (6.5%)	0 (0.0%)	
Adverse event	25/342 (7.3%)	26/372 (7.0%)	2/46 (4.3%)	1/7 (14.3%)	
Death	10/342 (2.9%)	10/372 (2.7%)	1/46 (2.2%)	0 (0.0%)	
Symptom stabilization	76/342 (22.2%)	73/372 (19.6%)	14/46 (30.4%)	0 (0.0%)	
Kidney transplant during follow-up, n (%)	97 (12.0%)	110 (12.9%)	7 (9.0%)	3 (13.6%)	NR
Dialysis during follow-up, n (%)	183 (22.6%)	202 (23.8%)	28 (35.9%)	7 (31.8%)	NR
Meningococcal infection, n (%)	3 (0.4%)	3 (0.4%)	0 (0.0%)	0 (0.0%)	NR

aHUS = atypical haemolytic uremic syndrome; DUSC = Drug Utilisation Sub-Committee of PBAC; IQR = inter-quartile range; NR = not reported; SD = standard deviation

Source: pre-PBAC response, pp4-5 [aHUS Registry Biennial Interim Report, Attachment 8; M11-001 Australian cohort demographic analysis _30Aug2022, Attachment 8; DUSC analysis Item 7.4 “Eculizumab for aHUS utilisation update” (<https://www.pbs.gov.au/industry/listing/participants/public-release-docs/2020-10/Eculizumab-utilisation-update-prd-2020-10v3-redacted.PDF>), October 2020; aHUS Registry data analysis performed for this response].

a Cut-off date of 5 July 2021 was used for the global aHUS registry biennial interim report (provided in Attachment 8 of the submission)

b Cut-off date of 1 August 2022 was used for the data extraction conducted for the pre-PBAC response

c For the registry data: If eculizumab treatment was restarted less than 6 weeks after the infusion stop date, the recent exposure was reset to 0. If eculizumab treatment was discontinued for less than 6 weeks and restarted, the time on-treatment was calculated based on the end date of infusion after the treatment restart (+ 3 weeks).

d East Asian patients include patients enrolled from Japan, South Korea and Taiwan

e The DUSC analysis (October 2020) reports date of death (DoD) data from listing in December 2014 to 20 March 2020 (N=298) and utilisation data since listing in December 2014 to the end of May 2020 (N=323). The full dataset comprises mostly adults 18 years and older (90.4%).

f For the 5 July 2021 data cut there are 19 patients with registry enrolment in 2012 vs the latest output, where 81 patients had first treatment in 2012, the numbers differ as these are two different variables and have thus been presented separately.

* Corrected from 0.92 in the pre-PBAC response

** Note that the results presented in Table 6 are derived from ad-hoc analyses conducted specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study M11-001. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Comparative effectiveness

6.14 The results from the studies are summarised in Table 7.

Table 7: Results of outcomes across the studies

	Ravulizumab		Eculizumab		
	311	312 No previous eculizumab ^a	C10-004	C08-002	C10-003
N	56	20	41	17	22
Complete response ^b n, (%) 95% CI	30 (53.6%) 39.6, 67.5	15 (75.0%) 50.9, 91.3	23 (56.0%) 39.7, 71.5	11 (65.0%) 38.0, 86.0	14 (64%) 40.7, 82.8
Complete TMA Response in East Asian patients, n (%)	4/15 (26.7%)	4/5 (80%)	NR	NR	NR
Time to complete response, days median 95% CI	86 42, 401	30 22, 88	57 2, 147	NR	64 7, 260
Platelet count $\geq 150 \times 10^9/L$ n, (%) 95% CI	47 (83.9%) 73.4, 94.4	19 (95%) 75.1, 99.9	40 (98%) 87.1, 99.9	14 (82%) 57, 96	21 (95%) 77.2, 99.5
LDH ≤ 246 U/L n, (%) 95% CI	43 (76.8%) 64.8, 88.7	18 (90%) 68.3, 98.8	37 (90%) 76.9, 97.3	14 (82%) 57, 96	18 (82%) 59.7, 94.8
$\geq 25\%$ improvement in sCr n, (%) 95% CI	33 (58.9%) 45.2, 72.7	16 (80%) 56.3, 94.3	NR	11 (65%) 38, 86	16 (73%) 49.8, 89.3
Dialysis at baseline ^c , n (%)	29 (51.8%)	7 (35%)	24 (58.5%)	5 (29.4%)	11 (50.0%)
Dialysis discontinuation in patients on dialysis at study entry, n/N (%)	17/29 (58.6%)	6/7 (85.7%)	15/24 (62.5%)	4/5 (80%)	9/11 (81.8%)
Patients who began dialysis during the study, n/N (%)	7/27 (25.9%)	0 (0%)	4/17 (24%)	2/11 (18.2%)	0 (0%)
Patients who began dialysis during the study and were on dialysis after 26 wk, n/N (%)	6/7 (85.7%)	NA	NR	NR	NA
Patients with ≥ 20 g/L increase in haemoglobin within 26 wk, n, (%)	40 (71.4%)	17 (85%)	25 (61.0%)	11 (65.0%)	15 (68.0%)
eGFR at baseline, mL/min/1.73m ² , Mean (SD) Median (range)	51.8 (39.2) 40 (2, 119)	108.5 (56.9) 108 (10, 244)	NR	NR	NR
Change of eGFR from baseline to 26 wk, mL/min/1.73m ² Mean (SD) (ravulizumab) or LS mean (95% CI) (eculizumab)	34.8 (35.5)	85.4 (54.3)	25.94 (19.45, 32.42)	NR	62.67 (47.28, 78.07)

Source: constructed during the evaluation from Tables 44, 45, 48, 53, 55, 56, 57, 58, pp109-110, 122-3, 134-5, 137 of the submission. sCr = serum creatinine; LDH = lactate dehydrogenase; CI = confidence interval; NR = not reported; NA = not applicable.

^a Patients with prior eculizumab treatment had normal or near-normal hematological and renal function parameters at baseline which remained stable during treatment.

^b Platelet count $\geq 150 \times 10^9/L$ and LDH ≤ 246 U/L and $\geq 25\%$ improvement in sCr at 2 separate assessments obtained at least 28 days apart, and any measurement in between, at any time during 26 wk initial treatment phase.

^c Definitions of baseline dialysis varied between studies; see paragraph 6.23.

- 6.15 There were too few deaths in the ravulizumab studies to estimate mortality meaningfully. That is, of 2 indicators used by PBAC to assess eculizumab versus best supportive care, only one, the surrogate marker of TMA response, is available for comparison of ravulizumab with eculizumab.
- 6.16 The frequency of a complete TMA response with ravulizumab was broadly similar to that observed with eculizumab although the submission noted that there was a lower likelihood of a complete TMA response in East Asian patients in Study 311: 4/15 (26.7%) vs 26/41 (63.4%). The reason for this difference is unclear. The submission attributed it to delayed treatment in East Asian centres, citing Menne, 2020, who reported the study as finding that ‘13 patients were recruited in Japan, Korea, and Taiwan. Only 2 of these 13 patients (15.4%) versus 28 of 43 patients (65.1%) recruited in other countries achieved a complete TMA response’, including 2/2 patients of Asian background enrolled in Europe. This is attributed to delayed initiation of treatment in Asian centres on the basis that 10/11 Asian patients in 311 who did not meet the criteria for a complete TMA response were treated later than 4 weeks after the beginning of the TMA episode, while both patients who did respond were treated within 4 weeks of the beginning of the TMA episode. However, the source of these data is not clear, and was not found in the CSR.
- 6.17 If the lower frequency of response in East Asian patients was due to delayed treatment, it should also affect results with eculizumab. Registry data held by the sponsor on the use of eculizumab in East Asia would be helpful in this regard. The pre-PBAC response provided updated registry data including 22 patients treated in East Asian centres (see Table 6). The rate of deaths in this subgroup was higher than the overall registry population but the subgroup is relatively small. However, a recent report of 79 adults with aHUS treated with eculizumab in Japanese centres found a complete TMA response in 35.3%. Given that it is usual for routine clinical use to result in worse outcomes than a formal study, this may be significantly greater than the proportion of Asian patients responding in 311.
- 6.18 Patients with a history of renal transplantation were less likely to have a complete TMA response with ravulizumab, although numbers were small: 2/8 (25%) vs 28/48 (58.3%).
- 6.19 The 3 studies of eculizumab had previously been considered by the PBAC. At its meeting in March 2014 the PBAC noted that mortality in the eculizumab studies was much lower than in any of the 6 available case series of patients not treated with complement inhibition. The PBAC also noted the results using the surrogate outcome of response in TMA, and concluded that ‘the claim of superior efficacy was supported’, but that ‘the magnitude of the incremental benefit compared to supportive care was difficult to determine with certainty’ (paragraph 9, Eculizumab PSD March 2014).
- 6.20 Data from the sponsor’s global registry provide additional information on the mortality rate with eculizumab treatment. A total of 1,882 patients were enrolled in the registry up to 5 July 2021. Of these, 1,205 (64.0%) were ≥ 18 years of age, and 677

(36.0%) were <18 years. Eculizumab was given to 1,276/1,882 (67.8%) patients, including 808/1,205 (67.0%) adult patients and 468/677 (69.1%) of paediatric patients.

- 6.21 There were 96 deaths among 1,265 eculizumab-treated patients with data available (7.7%), compared to 66 deaths among 598 patients not treated with eculizumab (11.2%) and eculizumab treatment was associated with little or no reduction of mortality (weighted hazard ratio (95% CI) 0.803 (0.589, 1.094)). The PSCR attributed the relatively small differences in mortality seen in the registry data to treated patients having more severe disease. The PSCR also noted this submission included data from Study C11-003 (Menne 2019); a prospective long-term follow-up study of 93 patients from earlier eculizumab trials (presented to the PBAC), 82 of whom had on-treatment periods during the conduct of C11-003. Based on data from over 5 years of follow-up (median 65.7 months), 3 deaths were reported, supporting the data previously evaluated by the PBAC.
- 6.22 The frequency with which dialysis needed at baseline could be stopped, and the frequency with which dialysis became necessary during treatment were also, broadly, similar between ravulizumab and eculizumab. However, the heterogeneity between the eculizumab studies noted by the PBAC (paragraph 7, Eculizumab, PSD, March 2014) also hampers interpretation of the dialysis outcomes in the ravulizumab studies.
- 6.23 The definition of baseline dialysis, in particular, was not the same in the eculizumab and ravulizumab series. In C10-003 and C10-004 the definition of baseline dialysis was between 7 days before and 14 days after the first dose of eculizumab; in C08-002 the definition was between 56 days before and 15 days after the first dose of eculizumab. In the ravulizumab studies, baseline dialysis was defined as within 5 days before treatment initiation. The effect of these differences is that patients who began dialysis soon after treatment initiation were counted as receiving dialysis at baseline in the eculizumab series but not in the ravulizumab series.
- 6.24 Other measured efficacy variables (haemoglobin, glomerular filtration rate, CKD stage) changed in step with resolution of TMA. In Study 311 and Study 312 fatigue scores increased rapidly, reaching a stable level by 10 weeks (i.e. before the median time to complete TMA response). Similar increases in fatigue scores were seen with eculizumab, but the timing of change was not reported.

Indirect treatment comparisons

- 6.25 The submission presented 2 indirect comparisons: a naïve (unanchored, unadjusted) indirect comparison and an unanchored adjusted indirect treatment comparison (aITC) of ravulizumab versus eculizumab using propensity score methodology. The submission relied on the latter as the primary basis for the comparison of ravulizumab and eculizumab for efficacy and the former for the assessment of comparative safety.

Naïve (unanchored, unadjusted) indirect treatment comparison

- 6.26 The naïve (unanchored, unadjusted) indirect comparison of ravulizumab and eculizumab compared the efficacy outcomes at 26 weeks in Study 311 (ravulizumab)

with those in Studies C10-004 and C08-002 (eculizumab) for adults, and separately, the outcomes at 26 weeks for Study 312 Cohort 1 (ravulizumab) and Study C10-003 (eculizumab) for paediatric patients. The outcomes evaluated were haematologic and renal endpoints and quality of life measures. The results used are shown in Table 7.

- 6.27 The submission noted differences between the datasets that reduce confidence in this comparison including differences in definitions of dialysis patients at baseline; use of adjunctive therapies; the age of patients; regional differences in trial locations; the dates of the different studies; and changing definitions of aHUS.
- 6.28 This is a broadly accurate description of the datasets and is discussed in more detail below. The resulting uncertainty in comparing the 2 treatments also applies to the interpretation of the aITC, see below.

Unanchored, adjusted indirect treatment comparison (aITC)

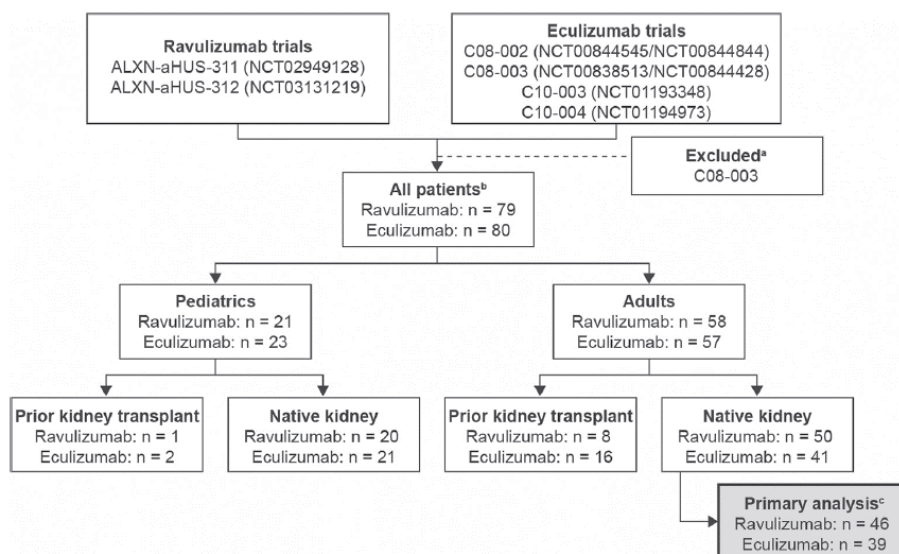
- 6.29 The description of the methods for the aITC as provided in the submission is summarised below.
- 6.30 Individual patient data from ravulizumab and eculizumab studies were pooled into a single data set. Data were available from 2 ravulizumab studies (Study 311 and Study 312) and 5 eculizumab studies (C08-002 A/B; C08-003 A/B; C10-003; C10-004; and C11-003). The primary analysis was confined to adults who had not had a renal transplant. Data from Study 312 and Study C08-002 were therefore excluded and C08-003 and C11-003 were excluded because they were long-term studies.
- 6.31 Propensity scores were calculated for each patient in the pooled analysis set. The variables used within the propensity score specification included: dialysis status; eGFR; platelet count; and LDH, selected as the most influential characteristics to balance between the 2 treatments for which data was available. The resulting propensity scores were used to balance those patient characteristics for which data was available between treatment groups. Statistical tests were performed after application of the stabilised weights to ensure that prognostic baseline characteristics were not significantly different at the $p < 0.1$ level before endpoints were revealed.
- 6.32 The usefulness of this approach depends on how well the variables used in the propensity score predict outcomes, and on the completeness of the data. As noted in the published version of the aITC (Tomazos, 2022), 'When interpreting the results [the reader] should note differences between treatment groups in characteristics for which it was not possible to balance using propensity scoring [...]. These include differences in clinical practice associated with the involvement of different countries and with the trials being conducted at different times. Additionally, time to complement inhibitor treatment – a strong predictor of renal function recovery [...] was inconsistently measured between studies, thus balancing could not be carried out on this parameter'.

- 6.33 There have been significant advances in understanding of aHUS since eculizumab became available, which would favour ravulizumab, and this alone makes interpretation of the aITC difficult.
- 6.34 Inability to adjust for time to treatment initiation is problematic because worse results in Asian patients treated with ravulizumab in Study 311 are attributed by the submission to delay in initiating treatment in Asian centres (see paragraph 6.16). No Asian centres contributed patients to the eculizumab series, and 23% of patients were of Asian background in ravulizumab studies, so the data do not allow comparison of eculizumab and ravulizumab in Asian centres.
- 6.35 The submission stated that data collected at 26 weeks were used for outcomes analysis ‘as this coincided with the primary endpoint in the studies’. The primary outcome required normalisation of platelet count and LDH and improvement in renal function at 2 separate assessments at least 4 weeks apart within 26 weeks of first treatment. The evaluation considered that the definitions of response in the study meant that patients who met the requirements for complete response at one time could fail to do so later, including at 26 weeks, but were still counted as complete responders. Further, meeting the criteria for complete response at Day 183 would not count towards the primary outcome in the original studies unless all the criteria were also met at 183-28 days and on any measurements in between. For the aITC analyses, the submission stated that a window of acceptability of ± 56 days around Day 183 was adopted for the confirmation of response. This was to account for patients who did not record a visit on Day 183 exactly, and to allow for maximum patient inclusion. The evaluation considered that this implied that the requirement that a complete response be sustained for 4 weeks to be counted was neglected for the aITC, and that patients meeting the criteria for complete response after 26 weeks (and within ± 56 days) could count towards the primary outcome in the aITC although they could not in the original studies. However, the PSCR stated that ‘the requirement that a complete response be sustained for 4 weeks’ was maintained in the aITC as ‘patients were still required to meet response criteria, at least 4 weeks apart’. The ESC considered it remained unclear whether the definition of response aligned between the studies and the aITC analyses, and noted that there was a large increase in reported time to complete TMA response between the original trials (Table 7) and the aITC (Table 8).
- 6.36 Definitions for clinical outcomes, including LDH and platelet normalisation, and creatinine improvement, and setting eGFR to a value of 10 mL/min/1.73m² for patients undergoing dialysis, were aligned with the ravulizumab clinical study for consistency. It was stated that for the purposes of the aITC, definitions of dialysis status were aligned as closely as possible based on the raw data available for the studies, but that differences remained. It was further stated that in the ravulizumab studies and eculizumab C10-003 and C10-004 studies, dialysis at baseline was defined as within 5 days before the first treatment dose, extending to 7 days before for the eculizumab C08-002 study, but this is incorrect. In C10-003 and C10-004 the definition

of baseline dialysis was between 7 days before and 14 days after the first dose of eculizumab, whereas in C08-002 the definition was between 56 days before to 15 days after the first dose of eculizumab. Differences also exist in the definition of dialysis at endpoint, which was aligned to definitions of within 5 days of endpoint for ravulizumab studies and within 7 days of endpoint for eculizumab studies, but few patients were on dialysis at the study endpoint.

- 6.37 Statistical testing was performed on both baseline and endpoint data. Treatment groups were compared using Welch’s two-way t-tests for continuous variables and χ^2 -tests were used to obtain p-values for categorical variables. Values between treatments were assessed for differences at $p < 0.1$ at baseline, and $p < 0.05$ at endpoint. Confidence intervals (CI) of the difference between ravulizumab and eculizumab were provided for all continuous variables, and CIs of the difference in proportions were provided for categorical variables with binary outcomes.
- 6.38 The ‘flow of patients’ that were included in the analysis of the aITC is shown in Figure 1 below and the results for the hematological outcomes at 26 weeks are shown in Table 8.
- 6.39 Figure 1 shows that nearly half of the patients in the studies were not included in the analysis. The smaller numbers and consequently wider CIs reduce the chance of finding differences between the cohorts to be statistically significant. Notwithstanding the statistical analyses used to adjust for potential confounding, the results of the analysis are likely to be biased because it was not possible to include in the propensity score some factors known to influence outcome, and those factors favour ravulizumab. The use of an outcome different from the primary outcome in the studies also makes the results difficult to interpret.
- 6.40 As an example of the difficulty in interpretation the change in outcome measure in the aITC creates, the median time to complete TMA response in the original studies favoured eculizumab: 86 days in Study 311, somewhat greater than the 57 days and 64 days in Studies C10-004 and C10-003 respectively (see Table 7), but in the aITC the mean time to complete TMA response favoured ravulizumab: 156 days vs 169 days with eculizumab, because of the use of Day 183 data to define the outcome.

Figure 1: Flow of patients in the adjusted ITC dataset



Source: Figure 10, p75 of the submission.

^a Data from eculizumab trial C08-003 were excluded owing to the study being conducted in a different patient population (patients were receiving long-term maintenance plasma therapy at baseline and, consequently, had normal platelet counts).

^b 'All patients' represents the maximum possible number of patients before the application of missing data restrictions for each subgroup by treatment.

^c Patient numbers for primary analysis represent patients with complete cases for propensity score variables, with a maximum of one missing laboratory measure and outcome data within 56 days of the 6-month endpoint.

Table 8: Results of the indirect comparison

		Eculizumab (N=39)	Ravulizumab (N=46)	p-value (95% CI) ^a
Effective sample size		39.0	46.0	
Complete TMA response	Yes	27.2 (70%); 54%-82%	26.2 (61%); 46%-74%	0.398 (-29% to 12%)
Platelet count				
Normalisation	Yes	37.6 (96%); 85%-99%	39.5 (92%); 80%-97%	0.391 (-14% to 6%)
Change from baseline	Mean (SD)	126 (98) [N=39]	122 (110) [N=43]	0.855 (-50 to 41)
LDH				
Normalisation	Yes	36.9 (95%); 83%-98%	38.3 (89%); 76%-95%	0.372 (-17% to 6%)
Change from baseline	Mean (SD)	-355 (553) [N=39]	-475 (592) [N=43]	0.344 (-372 to 131)
Haematologic normalisation	Yes	35.5 (91%); 78%-97%	35.8 (83%); 69%-92%	0.294 (-22% to 7%)
Time to complete TMA response, days	Mean (SD)	169 (167)	156 (174)	0.728 (-88 to 62)

Source: Table 69, p164 of the submission. CI, confidence interval; LDH, Lactate Dehydrogenase; SD, standard deviation; TMA, thrombotic microangiopathy.

^a Represents the 95% CI of the mean difference between treatments for continuous variables, and the 95% CI of the mean difference in proportions for categorical variables. For categorical variables, 95% CI are only presented for binary outcomes. Percentages may not sum to 100% due to rounding. The number of patients available for the change in and improvement endpoints may be fewer than the number of patients with values at endpoint, as these outcomes require observations at both baseline and 26-weeks.

Comparative harms

6.41 A summary of the safety data reported in the studies is in Table 9.

Table 9: Summary of key adverse events in the studies, including extension phase

	Ravulizumab			Eculizumab		
	311	312		C10-004	C08-002	C10-003
		No prior eculizumab	Prior eculizumab			
N	58	24	10	41	17	22
Duration of treatment						
Mean weeks (SD)	95.9 (51.3)	94.4 (62.5)	107.6 (3.8)	57.4 (30.6)	97.6 (57.3)	23.9 (5.8)
Median weeks (range)	114.1 (0.6, 162.4)	126.3 (1, 154)	106.1 (102.3, 114.1)	51.7 (12.6, 125.1)	100.3 (2.0, 185.7)	25.6 (0, 26.5)
Patients with any AE, n (%)	58 (100%)	23 (95.8%)	10 (100%)	41 (100%)	17 (100%)	20 (90.9%)
Patients with AE assessed as drug related ^a , n (%)	21 (36.2%)	12 (50%)	2 (20%)	17 (41.5%)	12 (70.6%)	10 (45.4%)
Patients with any SAE, n (%)	36 (62.1%)	16 (66.7%)	1 (10%)	19 (43.6%)	17 (100%)	13 (59.1%)
Patients with AE resulting in drug discontinuation, n (%)	3 (5.2%)	2 (8.3%)	0 (0%)	1 (2.4%)	3 (17.6%)	1 (4.5%)
Patients with AE Grade 3 or higher, n (%)	52 (89.7%)	12 (50%)	1 (10%)	35 (85.4%)	13 (76.4%)	15 (68.2%)
Deaths, n (%)	4 (6.9%)	0	0	0	0	0
Discontinuation before 26 weeks, n (%)	9 (15.5%)	7 (29.2%)	0	3 (7.3%)	2 (11.8%)	3 (13.6%)
Discontinuation to latest follow-up, n (%)	28 (48.3%)	11 (45.8%)	0	11 (26.8%)	7 (41.2%)	6 (27.3%)

Source: constructed during the evaluation from Tables 30, 61 and 64, pp 72, 142, 148, p151, and 157 of the submission.

AE = adverse event; SAE = serious adverse event

^a Possible, probable or definite relationship to drug.

- 6.42 There were no clear-cut differences in adverse events between the eculizumab studies and the ravulizumab studies. Serious adverse events and discontinuations before 26 weeks may have been higher with ravulizumab. Discontinuations during open-label follow-up appear to have been higher with ravulizumab, but this could reflect development of clinical practice (in the DUSC analysis, treatment duration with eculizumab has declined with time).
- 6.43 Although the number of deaths in Study 311 was relatively high, one patient died of a stroke which occurred before treatment; 2 were over 70 years of age, had sepsis and required mechanical ventilation at baseline, and died of septic shock; one had Stage 5 kidney disease before enrolment and died of intracranial haemorrhage. It seems unlikely that these deaths represent a safety signal.
- 6.44 The ESC revealed experience in clinical practice with ravulizumab in PNH has resulted in some cases of breakthrough haemolysis in weeks 6 or 7, prior to patients receiving their next dose at week 8. It is unclear whether similar issues of treatment waning in weeks leading up to week 8 will be experienced in aHUS and what the consequences may be. The sponsor hearing indicated no evidence of breakthrough disease in aHUS in practice (see paragraph 6.2).

Benefits/harms

- 6.45 A benefits and harms table was not presented as the submission made a claim of noninferiority.

Clinical claim

- 6.46 The submission described ravulizumab as noninferior in terms of effectiveness and safety compared with eculizumab.
- 6.47 The evaluation considered that the therapeutic conclusion was not adequately supported because of the limitations in the quality of the evidence. However, the ESC noted complete TMA response was broadly similar for ravulizumab and eculizumab.
- 6.48 The ESC also noted and agreed with the PSCR, which reiterated that ravulizumab shares over 99% amino acid sequence homology with eculizumab, targets an identical C5 epitope motif, and accordingly exhibits identical mechanisms of action leading to rapid, complete, and sustained inhibition of C5. The PSCR argued the biological heritage of the molecules further supports the plausibility that ravulizumab and eculizumab produce similar efficacy and safety outcomes in the treatment of aHUS.
- 6.49 The PBAC considered that the claim of noninferior comparative effectiveness was uncertain, but reasonable based on biological plausibility and the limited data available in the context of a rare and life-threatening disease.
- 6.50 Similarly, the PBAC considered that the claim of noninferior comparative safety was uncertain but reasonable.
- 6.51 The PBAC considered that the original uncertainties it had observed with respect to the clinical data for eculizumab made the interpretation of the clinical data compared with ravulizumab particularly challenging.

Economic analysis

- 6.52 The submission presented a cost minimisation approach (CMA), described as a 'stepped CMA':
- Step 1 – establishing the PBS and MBS cost for eculizumab for adults based on the recommended dose in the Product Information, then calculating the price of ravulizumab using the recommended dose in the Product Information and the weight of patients in Study 311 (base case) and the aHUS registry (alternative). Alternative analyses using patient weight from a 2022 DUSC Secretariat analysis were conducted during the evaluation, but using the patient weight distribution from Study 311 resulted in the most conservative ravulizumab price.
 - Step 2 – using the same methodology described above, establishing the cost of eculizumab in paediatric patients, and therefore the prices of ravulizumab using patient weights from Study 312 (base case) and the aHUS registry (alternative).
 - Step 3 – weighting these prices according to the proportion of adult and paediatric patients in the treated population using the 2020 DUSC analysis.
 - Step 4 – applying a price reduction to the cost of ravulizumab by assuming $x\%$, which reduced the resulting per vial price of ravulizumab by $x\%$.
- 6.53 The CMA used the doses recommended in the Product Information documents, not the doses used in the studies, as the study reports did not provide the actual dose

used (see paragraph 6.10). This approach assumes not only equivalent efficacy for the recommended dose of ravulizumab, but also that treating clinicians will always use the recommended dose. The ESC agreed with the evaluation that, in clinical practice there may be instances where patient weight is rounded up to the higher dose option. Given this is a life-threatening disease the likelihood of rounding-up body weights or using the next higher category for patients near the top of the band, is very high because the consequences of giving too little likely outweigh the consequences of giving too much.

- 6.54 Both ravulizumab and eculizumab have weight-based loading doses, followed, in the case of eculizumab, by weight-based dosing in children up to 40 kg and a fixed dose in adults and children over 40 kg, and in the case of ravulizumab by weight-based dosing in both children and adults.
- 6.55 The results of the CMA depend on the weight of the patients treated, especially among adults (the great majority of patients). The submission used 2 sources of data for patient weights: firstly, Study 311 for adults and Study 312 for children, and secondly, from Australian patients in the global Alexion aHUS Registry, although only 4 children in the registry had weight recorded. The evaluation conducted an additional sensitivity analysis, using weight data for the treated eculizumab patients based on an analysis completed by the DUSC Secretariat using data extracted from the PBS database (provided to the evaluator 24 November 2022). The different weight distributions are shown in Table 10 below.
- 6.56 The submission selected a one-year time horizon for estimating the equi-effective dose as the mean treatment duration with eculizumab from a DUSC Secretariat analysis (provided to the sponsor in October 2022) is 384.79 days. The submission also provided estimates for a 2-year time horizon for adults only. The 2 year time horizon corresponded to the PBAC's advice for the PNH submission (July 2021) and also to the treatment duration in the requested restriction (see Table 3). However, as noted in the submission the one-year time horizon is more conservative.
- 6.57 The following information, key calculations and results for the CMA are provided in Table 10.
- Dosing frequency, number and amount of loading and maintenance doses for ravulizumab and eculizumab.
 - As discussed in paragraph 6.55, weight distributions for Study 311 (base case), the aHUS Registry and DUSC Secretariat analysis.
 - Equi-effective doses based on Study 311 (base case), as well as the aHUS Registry and DUSC Secretariat analysis;
 - Drug and administration cost for eculizumab and resultant cost-minimised prices for ravulizumab;

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- Costs for paediatric patients and weighted adult and paediatric pricing. The weighted adult and paediatric price, with the cost of the |, is the submission's base case result and is the source of the requested drug price.
- Cost-minimised price with cost of the [REDACTED] removed, which reduces the per vial price of ravulizumab by |% over the one-year duration used in the CMA. This is equivalent to | weeks of therapy, and, according to the sponsor, thus ensures that a large proportion of patients will not be inpatients at the time of the | dose.

Table 10: Cost minimisation of eculizumab and ravulizumab – summary one year time horizon

	Ravulizumab				Eculizumab
Dosing structure - adults	Weight-based				Fixed
Dosing frequency	1 loading dose, 8 weekly maintenance starting 2 weeks after loading dose				Loading dose weekly for 4 weeks, followed by fortnightly beginning week 5
Dose – loading phase and maintenance phase		Loading	Maintenance		Loading: 900 mg weekly for 4 weeks Maintenance: 1,200 mg fortnightly
	≥40 kg to <60 kg:	2,400 mg	3,000 mg		
	≥60 kg to <100 kg:	2,700 mg	3,300 mg		
	≥100 kg:	3,000 mg	3,600 mg		
Patient weight distribution		Trial 311	Registry	DUSC	NA
	≥40 kg to <60 kg:	19.3%	38.82%	23.4%	
	≥60 kg to <100 kg:	71.9%	58.82%	65.2%	
	≥100 kg:	8.8%	2.35%	11.3%	
Total mg's, 12 months (ravulizumab = proportion × dose)	Loading dose	2,669 mg	2,591 mg	2,661 mg	3,600 mg
	Maintenance dose	3,269 mg	3,191 mg	3,260 mg	28,800 mg
Total administrations, 12 months	Loading dose	1	1	1	4
	Maintenance dose	6.25	6.25	6.25	24
Equi-effective dose		23,097 mg	22,532 mg	23,039 mg	32,400 mg
Costing					
Drug cost					\$5,640.63: 300 mg vial
Administration cost					\$46.15: MBS item 105
Total drug cost	Cost-minimised: \$				\$609,188
Total admin cost	\$334				\$1,292
Total cost	Admin removed: \$				\$610,480
Cost-minimised pricing					
		Study 311	Registry	DUSC	
Per mg		\$	\$	\$	\$18.80
Per vial	300 mg vial	\$	\$	\$	
	1,100 mg vial	\$	\$	\$	
Paediatric patients					
Cost	Admin removed: \$				\$252,850
Per mg		\$	\$	NR	
Per vial	300 mg vial	\$	\$		
	1,100 mg vial	\$	\$		
Weighted adult and paediatric pricing (adults 90.4%, paediatric 9.6%; weighted = \$ per mg)					
Per mg	Adult	\$			
	Paediatric	\$			
Per vial	300 mg vial	\$			
	1,100 mg vial	\$			
Price reduction – removed (base case proposed in submission)					
		Adult	Paediatric	Weighted	
Cost-minimised price		\$	\$	-	
Per mg		\$	\$	\$	
Per vial	300 mg vial	\$	\$	\$	
	1,100 mg vial	\$	\$	\$	

Source: Table 110, p228; Table 112, p229; Table 113, p230; Table 115, p231; Table 117, p231; Table 119, p232; Table 121, p233; Table 122, p234; Table 123, p234; Table 124, p235 of the submission.

NA = not applicable; NR = not reported

6.58 The submission estimated that the equi-effective doses for adults were: ravulizumab 23,097 mg (7.25 infusions including the loading dose), over one year and eculizumab

32,400 mg (28 infusions including loading doses) over one year, based on the weight distributions from Study 311.

- 6.59 For adults, the cost per mg was similar between the submission's base case from Study 311 and the DUSC data, at \$█ per mg and \$█ per mg, respectively, while the Registry-based cost per mg was higher at \$█. When these costs per mg were applied to vial cost, the 300 mg vial cost differed by less than \$200 across the 3 sources.
- 6.60 The weighted adult/paediatric price lowered the estimated vial price slightly (compared with the adult price), to \$█ compared to \$█ for the 300 mg vial, and \$█ compared to \$█ for the 1,100 mg vial in the submission's base case. Removing the cost of the █ dropped the estimated prices considerably, to \$█ for the 300 mg vial and \$█ for the 1,100 mg vial. These latter two prices form the submission's requested effective prices for ravulizumab.
- 6.61 The submission relied on the weight of 4 paediatric patients from Study 312 (conducted in patients aged under 18 years) to calculate drug usage and cost for paediatric patients. It appears these were 4 patients that had been treated with ravulizumab, and since the remaining patients in that study cohort had weight greater than 40 kg, they were excluded. The submission did not supply patient weight data, so the values used could not be confirmed during evaluation. The PSCR provided patient weight data from Study 312 and stated that an error was made in the submission's CMA calculations with not all patients having been included. The PSCR provided a sensitivity analysis using the corrected data (data available for 28 paediatric patients, with the PSCR using data for the 21 patients who weighed less than 40 kg), which increased the price by around 0.6% (refer to Table 11). The PSCR stated that 'this analysis was provided for illustrative purposes only (and to demonstrate the negligible impact varying weight has on the overall price) and is not a requested change to the submitted price'.
- 6.62 Results of key sensitivity analyses are shown in Table 11.

Table 11: Sensitivity analyses for the cost-minimisation

	Ravulizumab – cost per mg	Difference versus base case
Base case (weighted adult/paediatric; cost for ██████████)	\$ ██████████	
Source for deriving patient weight (base case: Study 311)		
• DUSC data	\$ ██████████	0.7%
• Registry	\$ ██████████	3.0%
• Updated data from Study 312 (paediatric patients), per the PSCR	\$ ██████████	0.6%
Time horizon (base case: 1 year)		
• 2 years (for adults only)	\$ ██████████	19.7%
Proportion of adult/paediatric patients (base case: 90.4% adults)		
• Adults 100% (given weight data for paediatric patients is less reliable)	\$ ██████████	0.5%
ESC analysis: Switching (base case: all patients are assumed to require eculizumab and ravulizumab loading dose/s)		
• All adult patients commence ravulizumab by switching from eculizumab ^a	\$ ██████████	-3.4%
• 50% of adult patients commence ravulizumab by switching from eculizumab ^b	\$ ██████████	-1.7%
• 90% of adult patients commence ravulizumab by switching from eculizumab ^c	\$ ██████████	-3.0%
ESC analysis: CMA based on DUSC 2022 analysis of use under each restriction ^d	\$ ██████████	-2.9%

Source: Table 124, p235 of the submission; Excel workbook 'Cost minimisation model workbook'.

^a Assumes no adult patients require eculizumab loading doses (i.e. comparison assumes all adult patients are in the maintenance phase of eculizumab), while all patients receive ravulizumab loading dose. Total adult dose of eculizumab is 31,200 mg per year (26 fortnightly maintenance doses of 1,200 mg) rather than 32,400 mg per year (4 doses of 900 mg weekly loading doses and 24 fortnightly maintenance doses of 1,200 mg). Loading dose calculations were not performed on the paediatric population given the small relative proportion of paediatric patients. Cells changed were: 'Adult' worksheet: cell B5 and B8 changed to 0; N10 changed to =52/2; N11 changed to =104/2.

^b Assumes 50% of adult patients are in the maintenance phase for eculizumab (i.e. do not require eculizumab loading doses). Based on (50%*\$████████) + (50%*\$████████). The financial estimates did not appear to estimate the proportion of all ravulizumab-treated patients who would have switched from eculizumab versus the proportion who would have initiated on ravulizumab; thus, a midway point of 50% was applied.

^c Assumes 90% of adult patients are in the maintenance phase for eculizumab (i.e. do not require eculizumab loading doses). Based on (90%*\$████████) + (10%*\$████████). As above, the proportion of 'switchers' did not appear to have been estimated in the financial estimates.

^d Based the proportion of use under each restriction from 2022 DUSC analysis; based on adult patients only. Assumes the following weeks of treatment per restriction phase, per the restriction proposed by the sponsor: Eculizumab: 'initial' 4 weeks; 'initial – balance' 20 weeks; 'initial – extended' 56 weeks; 'continuing' 24 weeks; 'continuing – extended' 24 weeks. Ravulizumab: 'initial' 2 weeks; 'initial – balance' 24 weeks; 'initial – extended' 56 weeks; 'continuing' 24 weeks; 'continuing – extended' 24 weeks. From the DUSC 2022 analysis, the proportion of patients who use each sequence was: Initial -> Initial – balance = 36.9%; Initial = 30.0%; Initial -> Initial - balance -> Initial – extended: 15.4%; Initial – balance = 9.2%; Initial -> Initial - balance -> Initial - extended -> Continuing = 4.6%; Initial -> Initial - balance -> Initial - extended -> Continuing -> Continuing – extended = 3.8% (re-weighted to exclude 'other'). Ravulizumab dosing is based on patient weights from Study 311 per the submission base case. Applies a ██████████% reduction to the ravulizumab vial price. The resulting adult price (\$████████ per mg) was then weighted for the submission's proposed price in paediatric patients, resulting in \$████████ per mg.

6.63 Table 11 includes two sensitivity analyses conducted by ESC which attempted to:

- account for patients who switch from eculizumab to ravulizumab. The ESC considered that when patients switch from eculizumab to ravulizumab, the comparison in the CMA should be: eculizumab without any loading doses (maintenance phase only) versus ravulizumab with a loading dose (the Product Information for ravulizumab states that a loading dose of ravulizumab should be administered for patients switching from eculizumab).
- calculate the total cost per patient based on the 'Sequence of Authority applications by treatment phase', from the 2022 DUSC analysis, and weighting utilisation by the proportion of patients who use each restriction type. This analysis accounts for differences in the dosing intervals of the 2 therapies (and

consequent differences in durations of treatment in the submission’s proposed restrictions) and for the likely patterns of use in clinical practice.

The ESC considered that the results of these 2 analyses were informative and the impact of each of these parameters should be accounted for in determining the price of ravulizumab.

6.64 There are multiple uncertainties associated with the CMA. Firstly, there is uncertainty with respect to the clinical data. Secondly, the data provided in submission do not allow determination of the dose actually used in the studies, so even if the comparison of treatments was accepted as valid, the dose-equivalence cannot be reliably determined. Thirdly, based on the pricing approach as described, where the aim is to have the equivalent price for ravulizumab and eculizumab, the cost of the products is dependent on the weight of patients and the actual use of the product in practice which are unknown.

6.65 A CMA must establish that the cost per patient for treatment with ravulizumab would be no more than the cost per patient of eculizumab. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

Drug cost/patient/year

Table 12: Drug cost per patient for proposed and comparator drugs

	Ravulizumab			Eculizumab		
	Trial dose and duration	Cost-minimisation	Financial estimates	Trial dose and duration	Cost-minimisation	Financial estimates
Mean dose	Study 311: Mean or median dose was not provided. Number of infusions ranged from 1 to 16, those with 10 or 12 infusions (both 13.8%) was greatest.	PI-based dosing with weight distribution from Study 311. 23,097 mg in adults Loading dose 2,669 mg x1 Maintenance dose 3,269 mg x6.25 (in adults)	Initiating patients: ██████ ² vials per year Maintenance patients: ██████ ² vials per year Patients switching from eculizumab: ██████ ² vials per year	Study C10-004; Study C08-002; Study C10-003: NR	PI-based dosing. 32,400 mg in adults Loading phase: 3,600 mg Maintenance phase: 28,800 mg (in adults)	Initiating patients: 108 vials per year Maintenance patients: 104 vials per year
Duration	Study 311: 95.9 weeks Study 312: 107.64 weeks	1 year	1 year	Study C10-004: 57.4 weeks Study C08-002: 97.6 weeks Study C10-003: 23.9 weeks	1 year	1 year
Cost per patient/year	NA	\$█████ ¹	\$█████ ¹	NA	\$609,188	\$605,149

Source: Table 61, p142 of the submission; Study 311 CSR; Study 312 CSR; Excel workbooks ‘Cost minimisation model workbook’; ‘Section 4 BIM’.

NA = not applicable; NR = not reported; PI = TGA Product Information

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² < 500

- 6.66 The cost per patient per year is less for ravulizumab (Table 12) due to the sponsor's provision of the █, which reduces the resulting price per vial of ravulizumab by █%.
- 6.67 Ravulizumab is available as a 300 mg vial and an 1,100 mg vial. The submission indicated that as the recommended doses of ravulizumab are multiples of 300 mg, the required dose can be made up using the 2 vial sizes without any wastage. This was reasonable, if the PI-recommended doses are applied in practice.

Estimated PBS usage & financial implications

- 6.68 This submission was not considered by DUSC. The key inputs for the budget impact estimation are shown in Table 13.

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Table 13: Key inputs for financial estimates

Parameter	Input						Source/notes
Overall treatment market size and ravulizumab uptake							
Use of eculizumab/ravulizumab	100% of eculizumab PBS eligible population						As per current treatment rates
Uptake - incident patients	60%						Ravulizumab Advisory Board meeting minutes
Uptake - prevalent patients switching	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	
	70%	70%	80%	90%	90%	90%	
Drug data (adult dosing assumed to apply to all patients)							
Ravulizumab dosage			Loading	Maintenance			Ravulizumab PI
	≥40 kg to <60 kg:		2,400 mg	3,000 mg			
	≥60 kg to <100 kg:		2,700 mg	3,300 mg			
≥100 kg:		3,000 mg	3,600 mg				
Ecuzumab dosage	Initial: (Weeks 1 to 4) – 900 mg weekly Maintenance: (onwards) – 1,200 mg in first week after initial phase, then 1,200 mg fortnightly						Ecuzumab PI
Weight distribution			Study 311	Registry	DUSC		Study 311.
	≥40 kg to <60 kg		19.3%	38.82%	23.4%		Patient weight data from Australian patients in the Alexion aHUS Registry population. DUSC Secretariat analysis provided in November 2022.
	≥60 kg to <100 kg		71.9%	58.82%	65.2%		
	≥100 kg		8.8%	2.35%	11.3%		
Vials per patient per year							
	Ravulizumab		Ecuzumab			Calculation for ravulizumab; ecuzumab PI.	
Initiating patients	300 mg vial: 1,100 mg vial:	1 1	108				
Maintenance patients	300 mg vial: 1,100 mg vial:	1 1	104				
Patients switching from ecuzumab	300 mg vial: 1,100 mg vial:	1 1	NA				
Loading dose for switch patients	300 mg vial: 1,100 mg vial:	1 1	NA				
Number of administrations per year by treatment phase							
	Ravulizumab		Ecuzumab			Ravulizumab PI and ecuzumab PI	
Initiating patients	1		28				
Maintenance patients	1		26				
Patients switching	1		NA				
Predicted public and private hospital split – ecuzumab and ravulizumab							
Public and private hospital split	86.64% public 13.36% private						PBS data for public/private hospital and patient category weighting 2021
Drug price – effective prices							
Ravulizumab	300 mg		1,100 mg			Requested effective price, based on CMA and also weighted for public/private hospital use	
Weighted adult and paediatric price	\$1		\$1				
Ecuzumab 300 mg	Current price		2025 price			pbs.gov.au, October 2022 and current price less PBS 10-year anniversary reduction from 1 April 2025	
Weighted for public/private hospital use	\$5,647.02		\$5,364.99				
MBS costs							
Cost per administration	MBS item 105: Fee: \$46.15; 85% benefit = \$39.25						October 2021 MBS Schedule

Source: Table 128, p238-241 of the submission.

aHUS = atypical haemolytic uraemic syndrome; CMA = cost-minimisation analysis; NA = not applicable; PI = product information

The redacted values correspond to the following ranges:

1 < 500

- 6.69 The submission proposed that ravulizumab will replace eculizumab therapy for a proportion of patients that currently meet the PBS criteria for eculizumab therapy and therefore calculated the cost offset associated with the reduction in eculizumab use. The submission noted that clinical experts estimated 90% to 95% of patients established on eculizumab would switch to ravulizumab when it became available on the PBS. But the submission applied an uptake rate of 70% in Years 1 and 2, 80% in Year 3 and 90% in Year 4 onward to allow time for clinicians to become comfortable with ravulizumab use, and also to reflect that not all current eculizumab patients would be suitable for ravulizumab therapy. Uptake of 70% to 80% is lower than the 90% to 95% estimated by clinical experts, although it has limited impact on the financial estimates.
- 6.70 The submission did not provide estimates of the number of administrations and scripts that would be substituted for eculizumab. Instead, the submission provided estimates of the total use and cost of eculizumab with and without the PBS listing of ravulizumab.
- 6.71 The evaluation considered the data sources used were reasonable, although the proportion of patients who will switch from eculizumab as well as the actual dosages used when switching, are sources of uncertainty. Another key source of uncertainty is the average doses that will be used in clinical practice given the average weight of the patient population is unknown (as discussed in the 'Economic analysis' section).
- 6.72 The submission also included estimated cost offsets to the MBS given an expected lower number of infusions per patient per year for ravulizumab than for eculizumab. The estimated cost offset was relatively small (under \$100,000 per year). These offsets are not included in Table 14, as reduced costs for specialist visits are not generally considered a saving to Government as they will be used by other patients.
- 6.73 As noted above, the weight of patients will determine dose and cost. However, because the number of patients treated is small, the total cost for ravulizumab is uncertain because even a few additional patients of higher body weight have a meaningful impact on total cost.
- 6.74 The overall estimated use and financial implications of listing ravulizumab are shown in Table 14.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of incident and prevalent patients treated ^b	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of ravulizumab 300 mg vials	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Number of ravulizumab 1,100 mg vials	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of ravulizumab						
Cost to PBS less copayments (\$)	█ ³	█ ³	█ ³	█ ⁹	█ ⁹	█ ⁹
Estimated financial implications for eculizumab (if ravulizumab is PBS-listed)						
Cost to PBS less copayments (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net financial implications						
Net cost to PBS for eculizumab if ravulizumab not listed (\$)	█ ⁵	█ ⁸	█ ⁸	█ ⁸	█ ¹⁰	█ ¹⁰
Total cost aHUS therapies ^a (\$)	█ ⁶	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁸
Net cost to PBS (\$)	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷

Source: Tables 129 and 130, p242; Table 134, p245; Table 139, p240; Table 140, p250; Table 143, p253; Table 148, p256 of the submission.

aHUS = atypical haemolytic uraemic syndrome

^a Total cost to PBS for ravulizumab and eculizumab (with ravulizumab PBS-listed) added together, net of patient copayment.

^b Calculated during evaluation from Table 134 of the submission.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$30 million to < \$40 million

⁴ \$20 million to < \$30 million

⁵ \$60 million to < \$70 million

⁶ \$50 million to < \$60 million

⁷ net cost saving

⁸ \$70 million to < \$80 million

⁹ \$40 million to < \$50 million

¹⁰ \$80 million to < \$90 million

6.75 While the submission estimated a net cost saving for the PBS listing of ravulizumab, there remains considerable overall cost for aHUS treatments. The following table provides Year 1, Year 6 and total cost over 6 years for ravulizumab and eculizumab.

Table 15: Estimated net cost of ravulizumab and eculizumab

	Year 1	Year 6	Total Years 1 to 6
Net cost of ravulizumab	1	5	8
Net cost of eculizumab if ravulizumab is PBS-listed (\$)	2	2	9
Net cost of ravulizumab and eculizumab – total aHUS therapy cost (\$)	3	6	10
Net cost of eculizumab if ravulizumab is not PBS-listed (\$)	4	7	11

Source: Table 139, p249; Table 140, p250; Table 141, p251; Table 142, p252 of the submission.

aHUS = atypical haemolytic uraemic syndrome

The redacted values correspond to the following ranges:

¹ \$30 million to < \$40 million

² \$20 million to < \$30 million

³ \$50 million to < \$60 million

⁴ \$60 million to < \$70 million

⁵ \$40 million to < \$50 million

⁶ \$70 million to < \$80 million

⁷ \$80 million to < \$90 million

⁸ \$200 million to < \$300 million

⁹ \$100 million to < \$200 million

¹⁰ \$300 million to < \$400 million

¹¹ \$400 million to < \$500 million

6.76 The submission estimated a cost to the PBS of ravulizumab of \$30 million to < \$40 million in Year 1 and \$40 million to < \$50 million in Year 6, for a total of \$200 million to < \$300 million over the first 6 years of listing for the PBS listing of ravulizumab.

6.77 When cost offsets for eculizumab are included, there was an estimated cost saving of approximately \$10 million to < \$20 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, for a total saving of \$70 million to < \$80 million over the first 6 years for the listing of ravulizumab.

6.78 Given the uncertainty around the patient weight data used in the submission, along with lower substitution of eculizumab than predicted (only 70% of prevalent patients in Years 1 and 2 instead of the 95% estimated by clinical experts), the financial estimates are highly uncertain.

Quality Use of Medicines

6.79 The submission described the pharmacovigilance activities required by the TGA to support the quality use of ravulizumab.

6.80 The submission described the risk of meningococcal infection with ravulizumab. The PI recommended that all patients must be vaccinated against meningococcal infections at least 2 weeks prior to administering the first dose of ravulizumab, and patients who initiate treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. The PBAC noted and agreed with the ATAGI's advice dated 22 February 2023, which supported the determination of meningococcal ACWY (MenACWY) and meningococcal B (MenB) on the National Immunisation Program to include patients treated with ravulizumab in addition to eculizumab.

Financial Management – Risk Sharing Arrangements

- 6.81 The submission proposed a market cap for eculizumab and ravulizumab, with Commonwealth Payment Thresholds based upon agreed financial estimates.

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation regarding the PBS listing of ravulizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) pending resolution of substantial restriction issues, and amendments to the cost-minimisation approach (CMA) and financial estimates. The PBAC noted that the submission's request for PBS funding of ravulizumab for public hospital inpatients was inconsistent with PBS policy. The PBAC also considered that the submission's CMA had several uncertainties which would need to be resolved to ensure the cost of ravulizumab would be no greater than that of eculizumab. The PBAC considered the estimated linear growth in utilisation over the forward estimates was not justified and that a risk sharing arrangement (RSA) with 100% rebate to cover the overall PBS cost of aHUS therapy with a C5 inhibitor would be required.
- 7.2 The PBAC advised that the initial ravulizumab restriction should include the administrative note, 'This drug is not PBS-subsidised if it is administered to an inpatient in a public hospital setting', consistent with restrictions for other drugs that are routinely initiated in a public hospital setting (e.g. midostaurin and blinatumomab). The PBAC considered that all initiations for aHUS treatment would take place in an inpatient setting, given the acute nature of patients presenting with this disease. As such, the continued PBS subsidy of eculizumab for public hospital inpatients would create a disincentive for the initiation of ravulizumab. It is likely that patients would be expected to initiate with PBS eculizumab, and then switch to ravulizumab (with its additional loading dose) upon discharge. Also, multiple inpatient admissions are expected. The PBAC requested that the Department develop amendments to aHUS restrictions: removing public hospital inpatient use for ravulizumab; allowing non-PBS patients who would have met the PBS criteria at time of initiation of C5 inhibitor therapy to transition to PBS subsidised therapy upon discharge from hospital; allowing patients who are responding to treatment to switch once between eculizumab and ravulizumab and vice versa (noting unlimited switching from ravulizumab to eculizumab would be permitted for pregnancy or breastfeeding); and permitting one switch to eculizumab for patients who have experienced treatment failure with ravulizumab. The PBAC also considered that the duration of therapy available under the ravulizumab and eculizumab restrictions should be more closely aligned. The PBAC also noted the pre-PBAC response's comments regarding the ongoing utility of ADAMTS13 testing in the diagnosis of aHUS, and agreed that this testing should be maintained in the aHUS PBS restrictions.
- 7.3 The PBAC noted the ESC concern that patients may require a reduced interval between maintenance doses to avoid waning of treatment effect, as has been

experienced in a small number of cases in the PNH setting where breakthrough haemolysis (BTH) is a risk (this was provided as anecdotal evidence by PBAC and also noted in the sponsor hearing that in the UK, <500 out of <500 ravulizumab patients had returned to eculizumab, although these were not associated with BTH). The PBAC considered the inclusion of a criterion that prohibits use of eculizumab in patients who have experienced ‘treatment failure’ with ravulizumab may restrict patients from appropriate treatment in such cases. Therefore, PBAC suggested that to avoid repeated treatment switching, as stated above in paragraph 7.2, that patients be offered one opportunity to switch from ravulizumab to eculizumab if they experience ‘treatment failure’ with ravulizumab.

- 7.4 The PBAC noted the Expert Reference Group is currently available to review certain applications for access to PBS-subsidised eculizumab for aHUS. The PBAC advised the Expert Reference Group should be consulted on the revised aHUS restrictions. The PBAC requested the Department then reconsider the ongoing need for the Expert Reference Group. The PBAC proposed that by implementing a RSA with a 100% rebate over an appropriate annual cap, the risk to the Australian Government of inappropriate use would largely be mitigated and it may no longer be necessary retain the services of the Expert Reference Group.
- 7.5 The PBAC noted that a grandfathering restriction was requested, however this was not provided by the sponsor. It was unclear how far through therapy patients would be when switching from non-PBS supply to PBS supply and consideration of the necessary criteria for this restriction was required.
- 7.6 The PBAC acknowledged the consumer comments, which highlighted expected quality of life benefits associated with the extended treatment duration of ravulizumab compared with eculizumab. The PBAC noted that this aligned with the submission’s assumption that most patients who are now on long-term treatment with eculizumab will switch to ravulizumab because of a preference for a longer dosing interval.
- 7.7 The PBAC accepted that eculizumab was the appropriate comparator, as ravulizumab was designed by re-engineering the eculizumab molecule to approximately quadruple the half-life of the drug, and accordingly exhibits identical mechanisms of action but with an extended dosing interval. Eculizumab is the only therapy specifically available on the PBS for aHUS.
- 7.8 The PBAC recognised that the clinical evidence presented to support the claim of noninferiority was subject to serious limitations, as it was based on single arm studies and weak indirect treatment comparisons (ITCs). The PBAC also considered that the original uncertainties associated with the size of the benefit of eculizumab compounded the uncertainty of the ITCs. Nonetheless, the PBAC acknowledged that head-to-head trials were unlikely to be feasible for this rare condition.
- 7.9 The PBAC considered that the claim of noninferior comparative effectiveness in terms of complete TMA response, normalisation of platelet count and LDH improvement in renal function was uncertain, but reasonable based on biological plausibility and the

limited data available in the context of a rare and life-threatening disease. Similarly, the PBAC considered that the claim of noninferior comparative safety was uncertain but reasonable.

- 7.10 The PBAC considered that the submission's CMA was subject to substantial uncertainties arising from the unknown trial-based equi-effective doses, the unknown weight of patients in clinical practice, and the unknown number of vials that will be administered per dose in practice. The PBAC noted that the Australian Government should not bear the financial risk of these uncertainties because the Australian population already has access to therapy that is at least as effective and safe. The PBAC noted that the patient weights derived from Study 311 were the most conservative scenario, but that the submission's CMA did not adequately account for patients who will switch from eculizumab to ravulizumab and incur an additional loading dose and nor did it adequately account for the different duration of therapies supplied under each restriction phase. The PBAC agreed with the ESC that these parameters should be accounted for in determining the price of ravulizumab.
- 7.11 The PBAC noted the considerable cost per patient per year of aHUS treatment and that a reduced price for ravulizumab was offered to account for in-patient use for the █. However as noted in paragraph 7.2, routine PBS supply does not cover use for public hospital in-patients.
- 7.12 The PBAC requested that the financial estimates be updated based on the revised cost-minimised price. The PBAC noted that the financial estimates did not appear to estimate the proportion of all ravulizumab-treated patients who would have switched from eculizumab versus the proportion who would have initiated on ravulizumab. This would assist in calculating a revised CMA price which accounted for treatment switching and the additional ravulizumab loading dose requirements. The PBAC also noted that the submission's projected linear growth in treated patients did not reflect the stabilisation of patient numbers noted in the 2020 DUSC review (see paragraph 2.4 and Table 14) and that this should be rectified as the listing of ravulizumab is not expected to grow the market. The PBAC considered an RSA would be required with an overall expenditure cap for aHUS at no increase to that projected for eculizumab, with 100% rebate over the annual caps.
- 7.13 The PBAC also recommended a change to the circumstances under which certain meningococcal ACWY (MenACWY) and meningococcal B (MenB) vaccines be made available as designated vaccines for the purposes of Section 9B of the *National Health Act 1953*. The PBAC recommended that the following vaccines should be made available as designated vaccines for patients treated with ravulizumab as well as eculizumab, and noted that this aligned with the ATAGI's advice:
- Meningococcal polysaccharide serogroups A, C, W-135 and Y conjugate – Nimenrix®
 - Meningococcal *Neisseria meningitidis*, Meningococcal polysaccharide serogroups A, C, W-135 and Y conjugate serogroups A, C, W and Y – MenQuadfi®

- Multicomponent meningococcal group B (4CMenB) – Bexsero®
- Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM197 Conjugate Vaccine (Men ACWY-CRM) – Menveo®

Outcome:

Deferred

8 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.

9 Sponsor's Comment

Alexion is committed to working with the PBAC and Department of Health and Aged Care to enable PBS reimbursement of ravulizumab for people with aHUS; an ultra-rare, life-threatening condition.

Addendum to the March 2023 PBAC Public Summary Document:

**4.02 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.**

10 Background

- 10.1 At the March 2023 PBAC meeting, the PBAC deferred their decision regarding the requested Section 100 Authority Required listing of ravulizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) pending resolution of substantial restriction issues, and amendments to the cost-minimisation approach (CMA) and budget impact model. The response to the deferral provided further information and sought to address the PBAC's concerns.
- 10.2 At the March 2023 meeting, the PBAC noted the aHUS Expert Reference Group was available to review certain applications for access to PBS-subsidised eculizumab for aHUS and advised it should be consulted on the revised aHUS restrictions for ravulizumab. Subsequently, PBAC representatives and members of the Department of Health met with the aHUS Expert Reference Group in May 2023 to discuss (i) no PBS subsidy with administration of ravulizumab to inpatients in a public hospital setting; (ii) treatment switching between eculizumab (more frequent dosing) and ravulizumab (less frequent dosing) and vice versa; and (iii) other issues such as admission to hospital for any reason while on a medication for aHUS.
- 10.3 At the March 2023 meeting, the PBAC considered that the following changes may address the outstanding issues without requiring re-evaluation:
- The requested ravulizumab PBS restriction should be amended to preclude use in public hospital inpatients, noting that PBS funding in these patients is inconsistent with PBS policy (paragraph 7.1).
 - The CMA should be amended with respect to specific uncertain parameters so that the Australian Government does not bear the financial risk of these uncertainties, given the Australian population already has access to therapy that is at least as effective and safe. The submission's CMA had several uncertainties which would need to be resolved to ensure the cost of ravulizumab would be no greater than that of eculizumab (paragraph 7.10).
 - The financial estimates should be adjusted to include an estimate for the proportion of all ravulizumab-treated patients who would switch from eculizumab

versus the proportion who would initiate on ravulizumab. Further, the PBAC considered the estimated linear growth in utilisation over the forward estimates was not justified and that a risk sharing arrangement (RSA) with 100% rebate to cover the overall PBS cost of aHUS therapy with a C5 inhibitor would be required (paragraph 7.12).

- 10.4 Table 16 summarises how the response to the deferral addressed each of these issues. The response to the deferral provided 2 scenarios for PBAC consideration: a Base case aligning with PBS policy of no PBS funding for public hospital inpatients; and Scenario 1, which would include PBS funding at a discounted price for initiation of ravulizumab under the same circumstances as eculizumab, which allows PBS funding for inpatients in both private and public hospital settings.

Table 16: Summary of changes made in the response to the deferral

PBAC PSD March 2023	Response to the deferral (Base Case) July 2023	Addressed?
Requested listing		
<p>The PBAC advised the atypical hemolytic uremic syndrome (aHUS) Expert Reference Group should be consulted on the revised aHUS restrictions (paragraph 7.4). Following this consultation, it was proposed the requested PBS restriction should be amended to preclude use in public hospital inpatients, noting that PBS funding in these patients is inconsistent with PBS policy. There would be associated flow on restriction criteria required, to (i) allow non-PBS patients to transition to PBS subsidised therapy upon hospital discharge; and (ii) allow patients to switch between eculizumab and ravulizumab and vice versa.</p>	<p>The response to the deferral broadly agreed with the intent of the restrictions provided by the Department, following input from the aHUS Expert Reference Group. The response to the deferral proposed that: (i) the ravulizumab restriction should broadly align with the eculizumab restriction, with the exception of the note 'ravulizumab is not PBS-subsidised if it is prescribed to an inpatient in a public hospital setting' for the base case option; (ii) unlimited switching between eculizumab and ravulizumab may occur based upon clinical judgement; (iii) treatment phases for ravulizumab should take the most conservative durations; (iv) non-PBS patients will be able to transition to PBS subsidised therapy upon hospital discharge.</p>	<p>Yes, for the base case. In relation to point (i), the PBAC re-iterated that inpatient prescribing of PBS-funded ravulizumab would be inconsistent with PBS policy and as such Scenario 1 was not under consideration.</p>
Cost minimisation approach		
<p>Uncertainty regarding trial-based equi-effective doses, weight of patients in clinical practice, and the number of vials that will be administered per dose in practice (paragraph 7.10).</p>	<p>The response to the deferral included the SAS output from the 311 trial, showing patient level data of treatment exposure. The analysis demonstrated the dose-equivalence relied upon in the March 2023 submission favours eculizumab, with exposure in the 311 trial lower than what was assumed in the March 2023 submission (which relied upon the Product Information dosing). The revised CMA remains unchanged from the March 2023 submission regarding the dose-equivalence. This approach was conservative.</p>	<p>Yes</p>

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PBAC PSD March 2023	Response to the deferral (Base Case) July 2023	Addressed?
CMA did not adequately account for patients who will switch from eculizumab to ravulizumab and incur an additional loading dose, nor did it account for the different duration of therapies supplied under each restriction phase (paragraph 7.10).	The response to the deferral included the additional loading dose in CMA for patients who will switch from eculizumab to ravulizumab and accounted for the different duration of therapies supplied under each restriction phase.	Yes
Financial estimates		
Did not appear to estimate the proportion of all ravulizumab-treated patients who would have switched from eculizumab versus the proportion who would have initiated on ravulizumab (paragraph 7.12).	The response to the deferral proposed that the additional loading dose requirements for the prevalent eculizumab population that will switch to ravulizumab will [REDACTED] with ravulizumab therapy will not result in additional cost to Government. [REDACTED] are then built into the price of ravulizumab for the proportion of patients that will initiate on eculizumab therapy and switch to ravulizumab in the future, so no further reduction is necessary.	Yes
Clarify projected linear growth in treated patients given that the listing of ravulizumab is not expected to grow the market (paragraph 7.12).	The response to the deferral applied a linear growth trend with increased patient numbers ([REDACTED] ¹ patients over 6 years) compared to the March 2023 consideration ([REDACTED] ¹ patients over 6 years).	No.
Risk sharing arrangements		
A risk sharing arrangement should be employed to cover the overall PBS cost of aHUS treatment with a C5 inhibitor therapy (paragraph 7.12).	The response indicated that the Sponsor is willing to enter into the specified RSA.	Yes

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

10.5 The text and tables below summarise the Base Case provided in the response to the deferral, and Scenario 1 where relevant.

11 Requested listing

11.1 The requested restriction in the response to the deferral had the following overarching elements in the Base Case:

- Inclusion of a note in the restriction to specify that ‘ravulizumab is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting’;
- Patients receiving non-PBS subsidised ravulizumab treatment who would have met the PBS criteria at time of initiation of C5 inhibitor therapy should be able to transition to PBS subsidised ravulizumab post-discharge;
- PBS subsidised public/private in-hospital patients initiated with eculizumab should be able to switch to PBS-subsidised ravulizumab post-discharge, and therefore facilitating treatment switching between PBS funded eculizumab and PBS funded ravulizumab is a key requirement for the restrictions of both eculizumab and ravulizumab.

11.2 As discussed in paragraph 4.5 of the March 2023 PSD, most patients who are currently on long-term treatment with eculizumab will switch to ravulizumab because of a preference for a greater dosing interval.

11.3 Table 17 summarises the changes made to the requested listing in the response to the deferral (Base Case).

Table 17: Summary of changes made in the response to the deferral (Base Case) with respect to the requested listing

PBAC PSD recommended change March 2023	Response to the deferral (Base Case) July 2023	Addressed?
Preclude use in public hospital inpatients, noting that PBS funding in these patients is inconsistent with PBS policy. The initial ravulizumab restriction should include the administrative note, "This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting".	The response proposed that the ravulizumab restriction should broadly align with the eculizumab PBS restriction, and add a note, "Ravulizumab is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting".	Yes
Align the duration of therapy available more closely under the ravulizumab and eculizumab restrictions.	The response proposed that the treatment phases for ravulizumab should take the most conservative durations, where appropriate.	Yes
Allow patients receiving non-PBS subsidised treatment with ravulizumab who would have met the PBS criteria at time of initiation of C5 inhibitor therapy to transition to PBS subsidised ravulizumab upon discharge from hospital.	The response proposed that a balance of supply or transition arrangement may be necessary.	Yes
Allow patients who are responding to treatment to switch once between eculizumab and ravulizumab and vice versa and permit one switch to eculizumab for patients who have experienced treatment failure with ravulizumab.	Following aHUS Expert Reference Group consultation, no limit on switching between C5 inhibitor therapies was proposed for consideration by the sponsor. The response to the deferral proposed that unlimited switching between eculizumab and ravulizumab may occur, based upon clinical judgement.	Yes.

11.4 The response to the deferral noted that a small number of patients who may initiate ravulizumab in a private hospital will have access to PBS-funded ravulizumab, as the note in the restriction would prohibit PBS-funded access to public hospital inpatients only.

11.5 The response to the deferral acknowledged with regard to **treatment initiation**:

- That a balance of supply or transition arrangement may be necessary to allow patients receiving **non-PBS subsidised treatment with ravulizumab** who would have met the PBS criteria at time of initiation of C5 inhibitor therapy to transition to PBS subsidised ravulizumab upon discharge from hospital;
- That patients in the public hospital system will **initiate treatment with PBS-subsidised eculizumab** and subsequently switch to PBS-subsidised ravulizumab post-discharge. Facilitating treatment switching between PBS funded eculizumab

and PBS funded ravulizumab is therefore a key requirement for the restrictions of both eculizumab and ravulizumab.

11.6 The response to the deferral stated with respect to **duration of therapy**:

- Initial and continuing treatment phases:

The extended initial and continuing treatment phases have been merged, although the continuing treatment phase duration for ravulizumab has been reduced to a maximum of 72 weeks (i.e., 9 x 8-weekly doses). While this is more conservative than 82 weeks proposed in the March 2023 submission (which was proposed to also include the 2-week loading dose for patients switching within this treatment phase), it is considerably shorter than the 80 weeks (56 weeks extended initial + 24 weeks continuing) of treatment currently in place for eculizumab.

The Secretariat noted that as the dosing requirements for ravulizumab are different in the loading dose and the maintenance dose, two separate restrictions are required to accommodate such a listing: one for a loading dose, and a balance of supply for the maintenance period which covers the required doses for this treatment phase.

- Recommencement treatment phase:

The Sponsor requested that the recommencement treatment phase allow for up to 26 weeks of treatment of ravulizumab (i.e., 1 x 2-week loading dose and 3 x 8-weekly maintenance doses). Given that recommencement of treatment should be considered analogous to initiating treatment with ravulizumab, a 26-week treatment duration would more appropriately align with the initial treatment phase for ravulizumab.

The Secretariat noted that 26 weeks of treatment with ravulizumab compares to 24 weeks of eculizumab in the same recommencement phase.

11.7 The response to the deferral stated with respect to **switching therapy** (p4):

That additional “switch from eculizumab” treatment phases aim to facilitate transitioning from eculizumab to ravulizumab. The concept of a separate switch restriction was proposed by the Secretariat for the March 2023 consideration. The intent of this switching restriction is to permit access to the 2-week loading dose of ravulizumab and facilitate switching from eculizumab regardless of how long patients have been taking eculizumab. To enable this switch to occur at the various treatment phases, three switch listings were proposed:

- during initial treatment (within the first 6 months of C5 inhibitor therapy prior to response criteria being assessed);
- during continuing treatment (once response criteria is assessed);
- during continuing recommencement of treatment.

- 11.8 The Secretariat noted that the outlined treatment switching phases proposed by the Sponsor only caters for the loading dose of ravulizumab and does not consider how to enable patients with further maintenance doses of ravulizumab. Furthermore, the addition of these three restrictions may be confusing and add another layer of complexity for prescribers to navigate. Adversely, this will also then flow onto eculizumab as three additional switching restrictions would be required.
- 11.9 The PBAC was asked to consider, for patients who are switching, whether the eculizumab administered immediately prior to switching would count to the duration of therapy needed before providing a response, i.e. the 24 (eculizumab) or 26 (ravulizumab) weeks of therapy per phase. This would alter the restrictions and require prescribers to apply clinical judgement in requesting the appropriate number of ravulizumab doses when switching.
- 11.10 The Secretariat noted that for patients who are switching, a previous application outlining eligibility to either the initial, continuing, or recommencement treatment of the previous C5 inhibitor would have been submitted to Services Australia. The PBAC was asked to advise whether any further documentation is required to be included in the switching criteria. If no further supporting documentation is required, the PBAC was asked to consider whether a lower authority level such as telephone/electronic would be suitable for immediate switching as this would provide a non-delayed authority approval.
- 11.11 The response to the deferral stated with respect to **grandfathered patients**:
- According to the Department’s proposed Grandfathering restriction, a Grandfathered patient can access up to 24 weeks of treatment before they must qualify under the Continuing treatment criteria for continued PBS access to ravulizumab. The wording of the Grandfathered restriction, as it is understood by Alexion, therefore permits a patient to access PBS ravulizumab if they are within the “initial treatment” period as well as the “continuing treatment” period. Therefore, in the event that a patient is in the “continuing treatment” period, i.e., received at least 26 weeks of non-PBS ravulizumab prior to PBS listing, then they would be required to demonstrate ongoing treatment response and not have experienced treatment failure, according to the clinical criteria proposed in the restriction.

For more detail on PBAC’s view, see section 13 PBAC Outcome.

12 Consideration of the evidence

Economic analysis

- 12.1 As a response to provide further information addressing the previous deferral, the economic analysis has not been independently evaluated.
- 12.2 At the March 2023 meeting, the PBAC stated (paragraph 7.10) that the submission’s CMA was subject to substantial uncertainties arising from:

- the unknown trial-based equi-effective doses;
- the unknown weight of patients in clinical practice (the PBAC noted that the patient weights derived from Study 311 were the most conservative scenario);
- the unknown number of vials that will be administered per dose in practice;
- not adequately accounting for patients who will switch from eculizumab to ravulizumab and incur an additional loading dose;
- not adequately accounting for the different duration of therapies supplied under each restriction phase.

The PBAC considered that these parameters should be accounted for in determining the price of ravulizumab.

- 12.3 The first 3 points listed above were unchanged from the March 2023 submission. Additional SAS data from Study 311 was provided in the response to the deferral detailing the patient level data of treatment exposure. The proposed equi-effective doses outlined in paragraph 6.58, based on the PI dosing and patient weights from Study 311, were more conservative in calculating the ravulizumab prices.
- 12.4 The revised CMA in the response to the deferral addressed both the additional loading dose required for treatment switching from eculizumab to ravulizumab, and the different duration of therapies supplied under each restriction phase.
- 12.5 The response to the deferral presented two scenarios for both the economic and financial impact analyses.
- 1) Base Case: reflects the inclusion of the note ‘This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting’ as drafted in the ravulizumab restriction. The Base Case includes the cost of the |of ravulizumab in the CMA.
 - 2) Scenario 1: largely consistent with the March 2023 submission, whereby the note is not included in the restriction, enabling ravulizumab to be available under the same circumstances as eculizumab. This analysis offsets the cost of |of ravulizumab in the CMA in acknowledgement of the exceptional funding circumstances (equating to |weeks of |ravulizumab treatment).
- 12.6 As the PBAC is unable to recommend PBS-subsidised public hospital inpatient use of ravulizumab (paragraph 7.1), the PBAC noted in this context that the Base Case scenario is the only acceptable economic option for consideration.
- 12.7 The Base Case CMA proposed in the response to the deferral is shown in Table 18. The resulting Base Case cost per vial was higher than the current PBS published price of ravulizumab. The response to the deferral proposed to reduce the cost minimised price of ravulizumab to |, representing a further |% reduction. Thus, the Base Case will provide savings to Government over the forward estimates. Given the Base Case pricing is |no Special Pricing Arrangement (SPA) was proposed for this listing.

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Table 18: Base case ravulizumab CMA

Steps		Cost per mg ^a	Notes
	March 2023 Base Case (adult)	\$█	The CMA was conducted based upon the average treatment duration in aHUS of one year. Given the treatment duration was informed by the same DUSC analysis as used to inform the restriction analysis performed during the evaluation, the results are very similar. No loading dose offset was factored for patients switching from ecuzumab to ravulizumab.
Restriction phase analysis			
	ESC sensitivity of Base Case	\$█	Analysis performed by the ESC during the evaluation and provided to the Sponsor, <i>Ravulizumab - Cost minimisation model workbook_CMA for restriction sequencing.xlsx</i> . See Table 11 above in Section 6.
Sponsor updated CMA analysis			
1	Initial-extended phase adjusted ^b	\$█	The Initial- extended phase was adjusted (from 56 weeks to 48), in line with the proposed restriction.
2	Initiation phase removed ^c	\$█	As ravulizumab will be used largely post ecuzumab initial phase (█), the initial phase of treatment in this analysis was not included. Requires re-weighting of the treatment phase proportions to exclude 'Initial' Category.
Loading dose offset			
	ESC sensitivity of Base Case	\$█	Analysis performed by ESC during the evaluation and provided to the Sponsor, <i>Ravulizumab - Cost minimisation model workbook_CMA for switching patients.xlsx</i> . See Table 11 above in Section 6.
Sponsor updated CMA analysis			
3	Loading dose applied to all post Initial patients ^d	\$█	All patients will initiate on ecuzumab, and of those that continue after the initiation phase (70%), a ravulizumab offset is applied. This was conservative and favours ecuzumab as not all patients will switch to ravulizumab. The proportion of initial phase patients remain removed from the analysis (as they will start and discontinue therapy on ecuzumab, so no accounting for ravulizumab therapy is required). The offset is achieved by assuming ecuzumab costs in the maintenance phase, compared to ravulizumab loading dose and maintenance costs.
Re-weighting for paediatric patients			
4	Weighted cost per mg ^e	\$█	The same price per mg was used for paediatric patients as proposed in the March 2023 submission base case (\$█ per mg) was used. This was then weighted adult/paediatric 90.4%/9.6% respectively to achieve the price per mg for both populations.
Resulting price per vial- Base Case CMA			
	300 mg		\$█
	1100 mg		\$█
Proposed pricing- Base Case (current published price of ravulizumab)			
	300 mg		\$6,574.12*
	1100 mg		\$24,105.11

Source: Item 6.12-ravulizumab-Ultomiris-Alexion Deferral response for July 2023 PBAC consideration Excel workbook 'Cost minimisation model workbook_Base Case'.

^a Includes administration cost

^b Cells changed were: 'Restriction type sequence' worksheet D44 changed to 48.

^c Cells changed were: 'Restriction type sequence' worksheet E6 changed to 0.

^d Cells changed were: 'Restriction type sequence' worksheet E34 changed to 0.

^e Calc: 90.4% x \$█ + 9.6% x \$█

* Published ex-man price as of July 2023 is \$6,574.12

Estimated PBS usage & financial implications

- 12.8 As a response to provide further information addressing the previous deferral, the estimated utilisation and financial implications have not been independently evaluated.
- 12.9 Table 19 summarises the financial impact for the Base Case scenario. The table also includes the March 2023 Submission financial impact of a ravulizumab PBS listing for comparison. Financial estimates have not been presented for Scenario 1 because this scenario is inconsistent with PBS policy.

Table 19: Financial impact to the PBS/RPBS with and without ravulizumab PBS listing - drug costs only, effective prices, Base Case

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of incident and prevalent patients treated	1	1	1	1	1	1
Without ravulizumab						
Total net cost of eculizumab	2	3	3	4	4	5
With ravulizumab						
Total net cost of eculizumab	6	6	6	6	6	6
Total net cost of ravulizumab	7	7	7	8	8	8
Total cost of aHUS therapies with ravulizumab	2	3	3	3	4	4
Total cost of aHUS therapies with ravulizumab with free loading dose for prevalent patients ^a	2	3	3	3	4	4
Savings associated with a ravulizumab PBS listing						
Difference with ravulizumab	9	9	9	9	9	9
With loading dose removed for year 1 switch patients	9	9	9	9	9	9
Financial estimates from the March 2023 PBAC consideration						
Number of incident and prevalent patients treated	1	1	1	1	1	1
Net cost to PBS	9	9	9	9	9	9

PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

Note: Numbers may not add due to rounding.

Source: Calculation details can be found in the provided Excel model, worksheet "Alexion BIM", Section 4 BIM Base Case.xlsx

Changes made to the 2023 submission model include:

Updated PBS data from 2021 to 2022 Calendar Year to establish predicted private/public patient category weighting.

Updated patient co-payments amounts (\$7.30 for concessional patients).

Updated extrapolation for patient estimates, based upon current Alexion order data.

Ravulizumab Price: Cells changes were: C19 to \$6,574.12, C20 to \$24,105.11.

Ravulizumab uptake rate for initiating patients: Cells changed were: C9 to 10%.

^a To determine the expenditure with ■■■ set Cells C177, 178 and 179 to 0 so that ■■■.

The redacted values correspond to the following ranges:

¹ < 500

² \$60 million to < \$70 million

³ \$70 million to < \$80 million

⁴ \$80 million to < \$90 million

⁵ \$90 million to < \$100 million

⁶ \$50 million to < \$60 million

⁷ \$10 million to < \$20 million

⁸ \$20 million to < \$30 million

⁹ net cost saving

- 12.10 The submission Base Case estimated a net cost saving to the PBS in Year 1 and in Year 6, summing to a total net cost saving over the first 6 years of listing. This compares to a total net cost saving over the first 6 years of listing for the March 2023 submission.

- 12.11 The response to the deferral stated that for the Base Case, the significant savings associated with ravulizumab reimbursement presented in the March 2023 submission are not realised as the [redacted], and ravulizumab use is far less due to the reduction in initiating patients (a 10% uptake for initiations is assumed). The response stated that nonetheless, there remains a cost saving for Government (net cost saving over 6 years) which due to the conservative nature of the ravulizumab CMA.
- 12.12 The estimated cost saving in Year 1 (only) is increased due to removal of the ravulizumab [redacted] for the prevalent eculizumab population. The response to the deferral stated that the loading dose cost will be captured in the [redacted] in Year 1. The response to the deferral stated that the estimates are artificially reduced to ensure the additional loading doses with ravulizumab therapy will not result in additional cost to Government. It was further stated that the loading dose is built into the price of ravulizumab for the proportion of patients that will initiate on eculizumab therapy and switch to ravulizumab in the future.
- 12.13 The financial estimates were updated in the response to the deferral with up-to-date order data. The response to the deferral stated that there has been largely consistent growth in aHUS patient numbers since eculizumab was reimbursed in 2014 and this trend was demonstrated in the submission considered in March 2023 with the inclusion of order data, which reflects the number of patients on therapy each month. The Sponsor stated that the extrapolated data compared to the actual data of the same period are accurate and supports the linear growth trend applied. Additionally, it was argued the 2022 DUSC data demonstrates linear growth, refuting the stabilisation of patient numbers claim made in the 2020 DUSC review. The response to the deferral stated that while ravulizumab will not grow the market, a level of projected growth in line with current evidence was appropriate.

Financial Management – Risk Sharing Arrangements

- 12.14 The response to the deferral stated that budget certainty is provided (at a lower expenditure level than projected for eculizumab) with an expenditure cap proposed [redacted]. The response stated that the cap negates all the financial risk to Government, particularly in terms of the concern related to spending more on ravulizumab than is currently the case with eculizumab with relation to weight ranges and greater loading doses being required due to the ability to switch between therapies in the restriction.

For more detail on PBAC's view, see section 13 PBAC Outcome.

13 PBAC Outcome

- 13.1 The PBAC recommended the Authority required (written) listing of ravulizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS), on the basis that it should be available only under special arrangements under the Section 100 – Highly Specialised Drugs Program, following its deferral at the March 2023 PBAC meeting. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of ravulizumab would be acceptable if it were cost-minimised to eculizumab and there was a Risk Sharing Arrangement to ensure no increase to the cost to Government for C5 inhibitor therapies for aHUS.
- 13.2 The PBAC had noted at the March 2023 meeting that funding of PBS medicines for public hospital inpatients is inconsistent with PBS policy and considered that ravulizumab should not be subsidised for admitted patients in public hospitals. The alternative Scenario 1 proposed in the response to the deferral was not considered appropriate by PBAC.
- 13.3 Following the March 2023 meeting, the PBAC sought advice from the aHUS Expert Reference Group to resolve issues for the aHUS PBS restrictions for C5 inhibitor therapies (ravulizumab and eculizumab); the advice informed the recommended PBS listing for ravulizumab in July 2023. The PBAC also considered that its additional prior concerns related to the CMA and the financial estimates were adequately resolved in the response to the deferral.
- 13.4 The PBAC has previously noted the clinical place of ravulizumab in patients with aHUS and the assumption that most patients who are now on long-term treatment with eculizumab will switch to ravulizumab because of a preference for a greater dosing interval (paragraph 4.5).
- 13.5 The PBAC noted the complexity of the requested ravulizumab restriction which includes long and complex criteria for different treatment phases. Although the proposed ravulizumab restriction generally aligns with the eculizumab PBS listing, the final wording will need to be resolved through further consultation with Services Australia and the sponsor with relevant flow-on changes to the eculizumab restriction.
- 13.6 The PBAC recommended the following with respect to the restriction:
- (i) All ravulizumab restrictions must include the administrative note, ‘This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting’;
 - (ii) Public hospital inpatients will be expected to initiate treatment for aHUS on eculizumab, and then switch to PBS-funded ravulizumab upon discharge. One loading dose of ravulizumab will be required at the time of switching and a balance of supply restriction is then required;
 - (iii) Private hospital inpatients can initiate treatment on PBS-funded ravulizumab and then will be able to continue ravulizumab treatment upon discharge;

- (iv) Following aHUS Expert Reference Group consultation, switching between C5 inhibitor therapies should not be limited as previously considered in March 2023 (see paragraphs 7.2 and 7.3) but instead be left to clinical judgement without limitations in the restrictions.
 - (v) Treatment switching between C5 inhibitor therapies could be considered in one restriction which covers all treatment phases rather than multiple listings as proposed in the response to the deferral. It will be necessary to include the loading dose and balance of supply restrictions for switching to account for the different durations of treatment allowed under each phase.
 - (vi) A written application for switching between aHUS therapies would be in line with other eculizumab and ravulizumab restrictions and would be appropriate even if no further documentation regarding treatment eligibility was required. The PBAC advised there was a risk that patients could otherwise receive additional weeks in each treatment phase if switching, noting this may impact whether treatment remained acceptably cost-effective given the high cost of the drugs. The PBAC considered that a written application would be appropriate as the aHUS patient population is small and it would not be unduly onerous on prescribers.
 - (vii) The duration of each treatment phase should be as closely aligned with eculizumab as possible, with the treatment phases for ravulizumab taking the most conservative durations, where appropriate. The PBAC noted the proposed reduced treatment duration for the initial and continuing phases was appropriate but also considered the extra two weeks of ravulizumab treatment in the recommencement phase was acceptable given the loading dose requirement (see paragraph 11.6).
 - (viii) A grandfathering restriction was deemed appropriate where patients would have met the initial restriction criteria at the time of initiating ravulizumab.
- 13.7 The PBAC noted that it had previously considered non-inferior effectiveness and safety of ravulizumab compared to eculizumab for the treatment of aHUS was reasonable at the March 2023 PBAC meeting (see paragraph 7.9). There was no clinical update for the July 2023 consideration.
- 13.8 The PBAC considered ravulizumab would be cost-effective on the basis of cost-minimisation to eculizumab. The PBAC noted the response to the deferral suggested the equi-effective doses provided in the March 2023 submission were conservative, relative to the patient-level data of treatment exposure in Study 311. As such, the PBAC accepted the equi-effective doses as outlined in paragraph 6.58. The equi-effective doses for adults were: ravulizumab 23,097 mg (7.25 infusions including the loading dose), over one year and eculizumab 32,400 mg (28 infusions including loading doses) over one year, based on the PI dosing and the weight distributions from Study 311.

- 13.9 The PBAC noted the CMA appropriately included the costs of switching and accounted for the different duration of therapies supplied under each restriction phase. Although the duration of treatment under each phase was based on a draft rather than final restriction, the PBAC considered the additional 1% price reduction to 1% would remove the risk that the final calculated prices for ravulizumab result in higher costs than eculizumab.
- 13.10 The PBAC considered that aHUS patient numbers will not increase with the PBS listing of ravulizumab and maintained that the 2020 DUSC review conclusion that eculizumab use for aHUS indicated it was a stable patient population was appropriate and use of the DUSC data was more relevant than the up-to-date order data provided in the response to the deferral. The PBAC did not consider the response to the deferral had adequately justified increasing the estimated number of patients eligible for C5 inhibitor therapy over the forward estimates compared to the March 2023 submission, which included a linear projected growth based on the DUSC review numbers (see Table 14 compared to Table 19).
- 13.11 The PBAC reiterated its March 2023 recommendation that a Risk Sharing Arrangement (RSA) to cover the overall PBS cost of aHUS treatment with a C5 inhibitor therapy with a 100% rebate would be required. The response to the deferral indicated that the Sponsor is willing to enter into the specified RSA.
- 13.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ravulizumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over existing treatment with a C5 inhibitor therapy, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 13.13 The PBAC noted flow-on changes to the eculizumab restriction are required.
- 13.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

14 Recommended Listing

This restriction is in the process of being finalised. The sponsor will be notified of the final restriction.

15 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.

16 Sponsor's Comment

The sponsor had no comment.