

## 7.09 ECULIZUMAB

### Solution concentrate for I.V. infusion

300 mg in 30 mL,

Soliris<sup>®</sup>, Alexion Pharmaceutical Australia Pty Ltd.

#### 1 Purpose of Application

- 1.1 The minor resubmission requested the PBAC to reconsider its July 2017 recommendation of an extension of the current Authority Required Section 100 (Highly Specialised Drugs Program) listing for eculizumab to extend the treatment duration for patients with atypical haemolytic uraemic syndrome (aHUS) in end stage renal disease (ESRD) who are eligible for a renal transplant.

#### 2 Requested listing

- 2.1 The resubmission sought an increase in the PBS-subsidised treatment duration in this setting from a maximum of three months (ten weeks of which would be PBS-subsidised), as recommended by the PBAC in July 2017, to a treatment duration of 12 months.
- 2.2 The resubmission also requested that public hospital inpatient treatment be funded by the PBS. The resubmission proposed a Risk Sharing Arrangement (RSA) whereby the sponsor would rebate [REDACTED] under this restriction. The resubmission stated that this would "[REDACTED]".
- 2.3 The pre-PBAC response revised the proposal such that the rebate ([REDACTED]) would apply to patients who [REDACTED] under this restriction, [REDACTED].
- 2.4 The minor resubmission requested that the restriction recommended by the PBAC in July 2017 (for eculizumab in patients with ESRD due to aHUS in the renal transplant period) be changed, per the listing below. The amendments proposed by the resubmission are marked in italics and strikethrough.

Public Summary Document - March 2018 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed for Max. Qty	Price	Proprietary Name and Manufacturer
ECULIZUMAB 300 mg/30 mL injection, 30 mL vial	1	0	\$5,937.50 (public) \$5,984.65 (private)	Soliris®	Alexion Pharmaceutical Australia Pty Ltd.

Abridged requested listing <sup>a</sup>	
<b>Category/ Program</b>	Section 100 – Highly Specialised Drugs Program
<b>Condition:</b>	Atypical haemolytic uraemic syndrome (aHUS)
<b>PBS Indication:</b>	Atypical haemolytic uraemic syndrome (aHUS)
<b>Restriction level:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Treatment criteria:</b>	Must be treated by a paediatric nephrologist OR Must be treated by a nephrologist AND Must be treated in a transplant unit.
<b>Clinical criteria:</b>	Patient must have had end stage renal disease caused by aHUS AND Patient must have undergone a renal allograft AND Patient must have a medium to high risk of recurrent aHUS in the allograft AND The treatment must be limited to a maximum duration of <del>40 weeks</del> 12 months.
<b>Administrative Advice</b>	At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug for up to <del>40 weeks</del> 12 months, according to the specified dosage in the approved Product Information (PI). <del>The first prescription will provide for up to two weeks' treatment with no repeats. The second prescription will provide for up to four weeks' treatment with one repeat providing for eight weeks' treatment.</del>

<sup>a</sup> The prescriber instructions and remainder of the administrative advice were unchanged from the restriction recommended by the PBAC in July 2017.

2.5 The pre-PBAC response revised the restriction. The key changes were to:

- facilitate use in the peri-transplant setting;
- provide separate initiating and continuing restrictions; and
- outline the duration of treatment and the number of repeats intended to be provided with each prescription (four weeks treatment with each prescription, with no repeats under the initial restriction and 11 repeats under the continuing restriction).

### 3 Background

3.1 Eculizumab was TGA registered on the 20 March 2009 for the treatment of patients with paroxysmal nocturnal haemoglobinuria to reduce haemolysis, and was approved for TGA registration for treatment of patients with aHUS on 3 October 2012.

3.2 This is the fifth submission for eculizumab to the PBAC for the treatment of aHUS.

**July 2017 PBAC consideration**

- 3.3 The most recent previous submission was considered in July 2017. The submission requested access to eculizumab for patients with aHUS in ESRD on chronic dialysis who are suitable for renal transplantation, and have a medium to high risk of subsequent thrombotic microangiopathy (TMA), without the requirement for evidence of active, progressive TMA, to prevent recurrence of TMA and graft loss.
- 3.4 Specifically, the submission requested initiation of eculizumab at the time of renal transplantation (peri-transplantation), and sustained access to eculizumab post-transplantation to protect the renal allograft. Further, the submission's proposed restriction did not exclude patients who have previously failed eculizumab.
- 3.5 In its consideration of that submission, the PBAC recommended extending the listing of eculizumab to include prevention of aHUS in patients at moderate-high risk of recurrence who have received a renal allograft for ESRD due to aHUS, irrespective of whether they have previously been successfully treated with eculizumab for aHUS (July 2017 PBAC Public Summary Document, para 7.1).

Treatment duration following renal transplant (in patients without active, progressive TMA)

- 3.6 The PBAC considered that initial treatment in this setting should be limited to 3 months of treatment post-transplant (comprising the period of inpatient treatment plus 10 weeks of treatment under the PBS) as this is the highest risk period for recurrence of aHUS. The PBAC noted that patients with recurrence of aHUS after this time would be eligible for eculizumab under the current listing (July 2017 PBAC Public Summary Document, paras 7.3 and 7.4).
- 3.7 The PBAC considered that while the data presented to support listing were not particularly robust, consisting of registry data, case series and international guidelines, it was satisfied that prophylactic treatment with eculizumab reduced the risk of recurrence of aHUS, while noting that it was difficult to quantify the level of risk reduction. The PBAC acknowledged that the clinical community as well as the general public was supportive of a listing for this patient group. (July 2017 PBAC Public Summary Document, para 7.5)
- 3.8 As part of its July 2017 consideration, the PBAC recalled the agreed outcomes of a clinical advice meeting that had been held on 12 February 2016 to discuss the place of eculizumab for the treatment of aHUS. These included the following points about ongoing eculizumab following renal transplantation:
- There was no clear consensus among the clinicians regarding the use of ongoing eculizumab as a prophylactic measure. Some clinicians would prefer to continue eculizumab indefinitely until the triggers of aHUS are better understood through further research. Others have developed experience with managing patients who have discontinued the drug and opted to monitor closely for any re-emergence of

the condition (by platelet count, haemoglobin, dipstick, etc).

- It was considered that clinical decisions about withdrawal of eculizumab may, in the future, be guided by high quality testing of complement function and increased understanding of the genetic basis for the disease. It was noted that complement function tests are not widely available at present, but genotyping was increasingly available.
- It was noted that during the first three months following renal transplantation, patients are exposed to numerous potential triggers for complement activation and aHUS recurrence in the post-surgery phase, including ischaemia-reperfusion injury and the use of calcineurin inhibitors. Patient management then changes from three months post-transplant, with a reduction in potential triggers encountered.
- The issue of alternative diagnosis for TMA in the post-transplant setting was discussed. It was noted that it can be challenging to distinguish aHUS from other differential diagnoses. For example antibody-mediated rejection may be present in a patient with thrombocytopenia and a kidney biopsy showing TMA. Complications of calcineurin inhibitor (CNI) treatment may also present a challenge to establishing an accurate diagnosis. It was conjectured that some transplant teams may choose to commence eculizumab treatment under such circumstances.
- Eculizumab would be administered as three further weekly doses of 900mg, with an increase to 1,200mg in the fifth week following transplant and ongoing dosing of 1,200mg every 14 days thereafter.
- It was noted that the dosing strategy for prophylaxis is the same as for acute management of aHUS, based on the expectation that the potential TMA triggers encountered post-transplant represent a comparable level of risk to an acute episode. The approved Product Information (PI) provides no specific direction on dosing in peri- or post-transplant settings. Since the TGA registration of eculizumab for aHUS in October 2012, there have been no published updates on the drug's pharmacokinetic or pharmacodynamic parameters. The absence of recent data to support dose, treatment frequency and treatment duration means that clinicians are forced to develop dosing strategies in the absence of robust evidence.

3.9 In July 2017, the new evidence that had been provided to support post-transplant and sustained use of eculizumab in patients after renal transplantation comprised data from 39 patients, reported in Siedlecki et al 2016 (global aHUS registry data) and Andrade 2016. In relation to this data, the July 2017 PBAC Public Summary Document noted that "the timing of initiation of post-transplant treatment was not reported in Siedlecki et al. 2016. It was also not reported if treatment was initiated prophylactically or after reoccurrence of aHUS. This along with a lack of detailed

information to allow for a more comprehensive comparison to the patients initiated peri-transplant reduced the value that can be placed on this data.” (July 2017 PBAC Public Summary Document, para 6.37)

#### Inpatient funding

- 3.10 The July 2017 submission had assumed that PBS subsidised treatment would be initiated as an inpatient and argued that, due to the need for timely access to eculizumab when a donor graft becomes available, pre-approval would be needed at the time the patient is activated on the deceased kidney donor list or once a living kidney donor transplantation is scheduled. This would enable drug delivery in advance of the transplant procedure (July 2017 PBAC Public Summary Document, para 2.3).
- 3.11 In its July 2017 consideration, the PBAC “considered that inpatient treatment should not be subsidised by the PBS” (July 2017 PBAC Public Summary Document, para 7.3).
- 3.12 In July 2016, the PBAC noted the report and conclusions of the Eculizumab Reference Group into the use of eculizumab in the first 12 months of the PBS aHUS listing. Amongst other matters, the PBAC considered that:
- utilisation of eculizumab was inconsistent with the intent of the Committee’s recommendations for the drug.
  - the larger than expected number of patients (73 vs ■■■) did not reflect a genuine excess of aHUS patients, noting the Reference Group’s conclusion that numerous patients who received eculizumab appear to have had TMA secondary to causes other than aHUS.
  - the potential for PBS subsidy of eculizumab for inpatients in public hospital was a contributing factor to the use of the drug in clinical scenarios beyond those recommended by PBAC based on clinical trial data. The PBAC considered that it would be reasonable for acute inpatient treatment to be initiated and funded by the public hospital, with PBS subsidy to commence once a PBS-eligible patient is ambulatory and has been discharged. (July 2016 PBAC Public Summary Document, paras 7.1, 7.2 and 7.7)
- 3.13 The July 2016 and July 2017 considerations aligned with the PBAC’s March 2016 consideration “that responsibility for subsidising eculizumab during hospital inpatient treatment would be a matter for the treating hospital. The PBAC noted that PBS subsidy would commence once a patient is discharged from hospital and once PBS eligibility is established as defined by the restriction criteria.” (March 2016 PBAC Public Summary Document, para 7.10).

#### **December 2015 PBAC consideration**

- 3.14 The PBAC recalled its December 2015 consideration of eculizumab for the treatment of active TMA in patients with aHUS, in which it recommended increasing the duration of treatment from 12 months to 24 months. Amongst other matters the

PBAC considered:

- “The PBAC recalled 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 two year follow-up data available at that time showed that there was no consistent improvement across all parameters in the 12 to 24 month period” (December 2015 PBAC Public Summary Document, para 5.5).
- “However, at the time PBAC also noted that it was not known whether any ongoing clinical improvement was due to the continued administration of eculizumab for two years, or represented the benefits of the drug within the first 6 to 12 months. For example, improvement could reflect the time elapsed since exposure to the trigger and resolution of the active TMA. Registry data available at that time showed that the risk of relapse was highest in the first 12 months following aHUS onset, but that patients have respond well to therapy when re-initiated” (December 2015 PBAC Public Summary Document, para 5.6).
- “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 PBAC therefore recommended that the PBS-subsidy arrangements be extended for a further 12-months period, to 24-months, to enable this review to occur” (December 2015 PBAC Public Summary Document, para 5.7).

### **Summary of changes**

- 3.15 Relevant details of the other previous submissions are outlined in the ‘Background’ of the previous Public Summary Document (July 2017, PBAC Public Summary Document, Paragraphs 3.3 to 3.9).
- 3.16 The new studies presented in the current resubmission which outline sustained, long-term use of eculizumab post renal transplant were: two retrospective case series; and two case reports. The resubmission also presented further data from the aHUS registry.
- 3.17 A summary of changes made between the July 2017 submission and the current resubmission is presented in Table 1.

Public Summary Document - March 2018 PBAC Meeting

Table 1: Comparison table between July 2017 submission and the current resubmission

	July 2017 submission	Current resubmission
Requested PBS listing	Patients with aHUS in ESRD on chronic dialysis who are suitable for renal transplantation, and have a medium to high risk of subsequent TMA, without the requirement for evidence of active, progressive TMA, to prevent recurrence of TMA and graft loss. <b>PBAC:</b> recommended 3 months of therapy in this setting; inpatient funding should not be subsidised by PBS	Requested a maximum of 12months treatment in this setting.  Requested PBS funding of inpatient use.
Requested effective DPMQ	• \$5,937.50 (Public)	• Same as previous.
Comparator	Resubmission claimed there was no PBS comparator. Included comparisons between PBACs suggested comparators of long-term dialysis, renal transplantation with prophylactic plasma exchange/infusion and treatment initiation at recurrence of active TMA post-transplantation.	No comparator stated. Presented data for patients who discontinued eculizumab post-transplant and historical outcomes (natural history) for patients with aHUS who underwent renal transplantation.
Clinical evidence	New studies submitted which include the use of eculizumab in patients with aHUS peri-transplant and long-term use after kidney transplantation: • Four new retrospective case series; • Data from the aHUS registry; • 4 new individual case reports. <b>PBAC:</b> data presented to support listing were not particularly robust (para 7.5)	New studies submitted which include long-term use of eculizumab post renal transplant: • Further data from the aHUS registry; • 2 retrospective case series; and • 2 case reports
Key effectiveness data	New evidence was provided for 98 who patients initiated eculizumab peri-transplant with a satisfactory allograft function maintained in 97% and with a TMA recurrence rate of 6%. Of 39 new patients initiated on eculizumab post-transplant 61% maintained satisfactory allograft function with a TMA recurrence rate of 42%. <b>PBAC:</b> data presented to support listing were not particularly robust (para 7.5)	The resubmission did not present aggregated outcomes from these data.
Clinical claim	Not explicitly stated. Assumed to be that eculizumab is effective in preventing post-transplantation recurrence of TMA and graft loss.	12 months of prophylactic eculizumab post-transplant was superior to 3 months followed by monitoring
Economic evaluation	None presented.	Same as previous.
No. of patients	Less than 10,000 patients in the first year decreasing to less than 10,000 per year from year 3	Same as previous.
No. of vials per patient	Less than 10,000 per year (weighted average dosing)	Less than 10,000 per year (full adult dosing)
Duration of eculizumab use	Assumed all patients would continue for the full forward estimates period <b>PBAC:</b> 3 months recommended	12 months
Estimated net cost to PBS	Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of \$20 - \$30 million over the first 5 years of listing (assuming continued treatment). <b>PBAC comment:</b> (Para 7.6) Not informative as they included continuing treatment beyond 10 weeks.	Less than \$10 million in Year 1 decreasing to less than \$10 million in Year 5 for a total of \$10 - \$20 million over the first 5 years of listing. Proposed RSA would lower the cost to \$10 - \$20 million over 5 years.

	July 2017 submission	Current resubmission
Risk sharing arrangement	Annual subsidisation cap proposed in Pre-PBAC response <b>PBAC comment:</b> (Para 7.6) RSA with hard cap would be appropriate (based on revised estimates with 10 weeks of treatment)	Annual subsidisation cap based on financial estimates provided. Rebate [REDACTED]

Source: Table 1, July 2017 Public Summary Document; text of the resubmission  
RSA = Risk sharing arrangement; TMA = thrombotic microangiopathy

## 4 Clinical place for the proposed therapy

- 4.1 The PBAC's July 2017 recommendation would enable patients with aHUS at medium to high risk of recurrence to receive three months of treatment post-transplant (comprising the period of inpatient treatment plus ten weeks of treatment under the PBS). Patients with recurrence of aHUS after this time would be eligible for eculizumab under the pre-existing listing.
- 4.2 The current resubmission proposed to extend the duration of prophylactic therapy to a maximum of 12 months post-transplant.

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

## 5 Comparator

- 5.1 The minor resubmission did not nominate a comparator. Based on the PBAC's July 2017 recommendation, the treatment that would be replaced is three months of eculizumab therapy post-transplant followed by re-initiation of eculizumab in the event of recurrence of aHUS.

## 6 Consideration of the evidence

### Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

### Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments outlined the risk of recurrence of aHUS following a renal transplant and the need to optimise post-transplant outcomes.

### Clinical evidence

- 6.3 The minor resubmission provided information relating to three circumstances:
- sustained use of eculizumab post-transplant (registry data, case series and case studies);

- renal transplant patients who discontinued eculizumab after at least ten weeks of treatment (case studies); and
- historical outcomes of renal transplantation in patients with aHUS. The interventions received by these patients were not stated, but were broader than prophylactic plasma exchange/infusion, which had been used as one of the comparators in the July 2017 submission.

6.4 The resubmission relied in part on studies and reports that had previously been presented in the March 2014, March 2016 and/or July 2017 submissions. Evidence that had not been previously assessed by the PBAC that was presented in the current resubmission included:

- Global aHUS Registry data (Vande Walle 2017), which comprised conference presentation slides. Information from the same data-cut had been provided in a conference abstract discussed in the July 2017 Pre-PBAC response;
- a pooled analysis (Legendre 2017) of four prospective clinical trials of eculizumab all of which have previously been assessed by the PBAC;
- two retrospective case series studies of sustained use of eculizumab post-transplant (Zuber 2017 and Levi 2017);
- four case reports: two outlined sustained use of eculizumab post-transplant (de Andrade 2017 and Brocklebank 2017); and two outlined discontinuation of eculizumab post-transplant (Krishnan 2017 and Levi 2017, the latter was also included in the case series studies);
- two new publications of historical outcomes in patients with aHUS who underwent kidney transplantation (Bresin 20016 and Noris 2013); and
- five position statements, consensus documents or review articles (four of which were referenced in the July 2017 Pre-PBAC response).

6.5 Details of the studies and case reports presented in the minor resubmission are provided in Table 2. The grey-shaded reports indicate those that have been seen by the PBAC previously.

**Table 2. Studies, case series and case reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Patients treated with eculizumab</b>		
<b>Global aHUS Registry Data</b>		
Vande Walle 2017	Van de Walle J, Siedlecki A, Isbel N, et al. Timing of eculizumab treatment and the need for dialysis in patients with aHUS undergoing kidney transplantation.	European Renal Association [17-A-1822]
<b>Pooled analysis of studies</b>		
Legendre 2017	Legendre C, Campistol J, Feldkamp T et al. Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis	Transplant International 2017; 30: 1275–1283
<b>Case series</b>		

Public Summary Document - March 2018 PBAC Meeting

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
Zuber 2017	Zuber J, Kamar N, Frimat M, et al. Breakthrough in the Management of atypical Hemolytic Uremic Syndrome after Kidney Transplantation: A Nationwide Study	European Society for Organ Transplantation (ESOT) Abstract OS271
Levi 2017	Levi C, Fremeaux-Bacchi C, Zuber J, et al. Midterm Outcomes of 12 Renal Transplant Recipients Treated with Eculizumab to Prevent Atypical Hemolytic Uremic Syndrome Recurrence	Transplantation 2017 (DOI: 10.1097/TP.0000000000001909)
Andrade 2016	Andrade, A. V., Machado, D., Souza, P. S., et al. Use of eculizumab for atypical haemolytic uremic syndrome in kidney transplantation - single centre experience in Brazil.	American Society of Nephrology (ASN) Kidney Week (PUB749)
Ardissino 2016	Ardissino G, Cresseri D, Giussani A, et al. Kidney Transplant in Atypical HUS: A Single Center Experience	American Society of Nephrology (ASN) Kidney Week SA-PO365
Kumar 2016	Kumar A, Stewart Z, Reed A, et al. Successful prophylactic use of eculizumab in aHUS kidney transplant patients: a report of 9 cases.	American Journal of Transplant, 16 (Suppl 3).
Sheerin 2016	Sheerin N, Kavanagh D, et al. A national specialized service in England for atypical haemolytic uraemic syndrome—the first years' experience	International Journal of Medicine, Volume 109, Issue 1, 1 January 2016, Pages 27–33
Matar 2014	Matar, D. et al. Atypical Hemolytic Uremic Syndrome Recurrence After Kidney Transplantation	Transplantation 98, 1205–1212 (2014).
Zuber 2012	Zuber, J. et al. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation.	Am. J. Transplant. 12, 3337–3354 (2012).
<b>Case reports</b>		
de Andrade 2017	de Andrade et al. Long-term outcomes of the Atypical Hemolytic Uremic Syndrome after kidney transplantation treated with eculizumab as first choice	PLoS ONE 12(11): e0188155.
Brocklebank 2017	Brocklebank et al. Factor H autoantibody is associated with atypical hemolytic uremic syndrome in the United Kingdom and Ireland	Kidney International (2017 ) 92, 1261–1271
Akchurin 2015	Akchurin et al. Preemptive use of eculizumab for living-donor kidney transplantation in a child with atypical hemolytic uremic syndrome	Einstein J. Biol. Med. (2015) 30:22-25
Riddell 2016	Riddell A., Goodship T, Bingham C. Prevention of recurrence of aHUS post renal trasplant with the use of higher-dose eculizumab.	Clin. Nephrol. 86, 200–202
Bouatou 2015 <sup>a</sup>	Bouatou at al. Atypical Hemolytic Uremic Syndrome recurrence after renal transplantation	Transplantation Direct 2015; 1 (2):1-4.
Coppo 2016 <sup>a</sup>	Coppo et al. Liver transplantation for aHUS: still needed in the eculizumab era?	Pediatr Nephrol (2016) 31, 759–768
Mallet 2015	Mallett A, Hughes P, et al. Atypical haemolytic uraemic syndrome treated with the complement inhibitor eculizumab: the experience of the Australian compassionate access cohort.	Intern. Med. J. 2015; 45 (10):1054-65.
Masengu 2015	Masengu A, Courtney A. Eculizumab for aHUS post transplantation: when and how to stop a good thing?	Transpl. Int. (2015). doi:10.1111/tri.12566
Parikova 2015	Parikova et al. Living-donor kidney transplantation for atypical haemolytic uraemic syndrome with pre-emptive eculizumab use	Transplant International (2015) 28: 366-369
Alasfar 2014	Alasfar S, Alachkar N. Atypical haemolytic uremic syndrome post-kidney transplantation: two case reports and review of the literature.	Frontiers in Medicine 2014; 1:52

Public Summary Document - March 2018 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
Ažukaitis 2014	Ažukaitis et al. Macrovascular involvement in a child with atypical hemolytic uremic syndrome	Pediatr Nephrol (2014) 29:1273-1277
Fehrman-Erkolm 2014	Fehrman-Ekholm I, Wadstrom J, et al. Eculizumab prevented recurrence of atypical haemolytic uremic syndrome in a kidney donor after a third kidney transplantation.	Austin Journal of nephrology and Hypertension 2014; 1 (4); 1019-21.
Ranch 2014	Ranch D, Crowther B, et al. Prophylactic eculizumab for kidney transplantation in a child with atypical haemolytic syndrome due to complement factor H mutation.	Pediatr Transplantation 2014; 18 (6):E189-9.
Bekassy 2013	Bekassy Z, Kristoffersson A, et al. Eculizumab in an anephric patient with atypical haemolytic uremic syndrome and advanced vascular lesions.	Nephrol Dial Transplant I2013; 28: 2899-2907.
Pelicano 2013	Pelicano M, de Cordoba S, et al. Anti-C5 as prophylactic therapy in atypical haemolytic uremic syndrome in living-related kidney transplantation.	Transplantation 2013; 96 (4): e26-e29.
Roman-Ortiz 2014 <sup>a</sup>	Roman-Ortiz et al. Eculizumab long term therapy for pediatric renal transplant in aHUS with CFH/CFHR1 hybrid gene	Pediatr. Nephrol. 2014; 29:149-153.
Tran 2013	Use of eculizumab and plasma exchange in successful combined liver-kidney transplantation in a case of atypical HUS associated with complement H mutation.	Pediatr. Nephrol. 2013; 29 (3):477-80.
Xie 2012	Xie et al. Tailored eculizumab therapy in the management of complement factor H-mediated atypical hemolytic uremic syndrome in an adult kidney transplant recipient: A case report	Transplantation Proceedings (2012) 44:3037-3040
<b>Patients who discontinue eculizumab post-transplant: Case studies</b>		
Krishnan 2017	Krishnan et al. Absence of thrombocytopenia and/or microangiopathic haemolytic anaemia does not reliably exclude recurrence of atypical haemolytic uremic syndrome after kidney transplantation	Nephrology (2017) 10.1111/nep.12937
Kasapoglu 2015	Kasapoglu et al. Prophylactic eculizumab use in kidney transplantation: A review of the literature and report of a case with atypical Hemolytic Uremic Syndrome	Ann Transplant, 2015; 20: 714-719
<b>Historical outcomes pre-eculizumab in patients with aHUS who underwent kidney transplantation</b>		
Bresin 2006	Bresin, E. et al. Outcome of renal transplantation in patients with non-Shiga toxin-associated hemolytic uremic syndrome: prognostic significance of genetic background.	Clin. J. Am. Soc. Nephrol. 1, 88–99 (2006).
Noris 2013	Noris, M. & Remuzzi, G. Managing and preventing atypical hemolytic uremic syndrome recurrence after kidney transplantation.	Curr. Opin. Nephrol. Hypertens. 22, 704–12 (2013).
Le Quintrec 2013	Le Quintrec, M. et al. Complement Genes Strongly Predict Recurrence and Graft Outcomes in Adult Renal Transplant Recipients with Atypical Hemolytic and Uremic Syndrome.	Am. J. Transplant. 13, 663–675 (2013).

aHUS = atypical haemolytic uremic syndrome

Source: Compiled from information provided in Table 4, pp27 -31

<sup>a</sup> Incorrectly referenced in minor resubmission, or referenced to a pre-publication version while a publication version had previously been referenced.

6.6 The PBAC also identified a case-series of patients with aHUS who underwent renal transplantation and did not receive prophylactic eculizumab therapy but instead had ‘rescue’ treatment available.<sup>1</sup> That is, patients were followed up with a protocol that

<sup>1</sup> Duineveld, Caroline et al. Living Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome: A Case Series . American Journal of Kidney Diseases, Volume 70, Issue 6 , 770 – 777. Accessed at [http://www.ajkd.org/article/S0272-6386\(17\)30836-3/fulltext](http://www.ajkd.org/article/S0272-6386(17)30836-3/fulltext)

limited eculizumab therapy to only those recipients with documented post-transplantation recurrence of aHUS. A total of 17 patients at high (16) or medium (1) risk of recurrence (due to genetic mutations) were followed-up for a median of 25 months (range 7 to 68 months). Only one patient had a recurrence of aHUS. The recurrence occurred 68 days after transplantation and was successfully treated with eculizumab. The PBAC noted that a potential limitation of the analysis was that all patients underwent living donor transplantation.

- 6.7 The PBAC also noted data from the Australia and New Zealand Dialysis and Transplant Registry that showed that clinicians perform renal transplantation on patients with haemolytic uraemic syndrome (HUS) despite eculizumab not being available for prophylactic use post-transplant. For example, the PBAC noted an analysis of 241 consecutive patients with end stage kidney disease secondary to HUS who commenced renal replacement therapy between 1963 and 2010.<sup>2</sup> Of the 241 patients with HUS, 130 (54%) received one or more renal transplants. Of these, 55% (72/130) received transplants from deceased donors. The PBAC noted the limitations of this study including that it did not distinguish between typical and atypical HUS. The PBAC also noted that data from over 50 years ago were included, and transplantation is more common in recent years.

### **Comparative effectiveness**

- 6.8 An issue raised in the July 2017 PBAC Public Summary Document was that “there was considerable heterogeneity between the various sources of evidence presented in the submission in terms of the baseline demographic and disease characteristics of the patients. Given this heterogeneity, and the potential for prognostic factors to confound the results, it was not appropriate to directly compare the outcomes between evidence sets and treatment regimes. Interpretation of the evidence was further hindered by the lack of uniformity in the outcomes reported, especially between the case series/reports and the clinical studies, and the time at which outcomes were assessed” (July 2017 PBAC Public Summary Document, para 6.33).
- 6.9 These limitations similarly applied to the new data presented in the current resubmission.

#### **i) Sustained use of eculizumab in patients after renal transplantation**

- 6.10 As noted above minimal data were available in the new studies supplied in support of this resubmission. The new data relating to sustained use of eculizumab in patients after renal transplantation are summarised in Table 3.

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<sup>2</sup> Tang, W. et al. End-stage kidney disease due to haemolytic uraemic syndrome--outcomes in 241 consecutive ANZDATA registry cases. *BMC Nephrol.* 13, 164 (2012). Accessed at <https://bmcnephrol.biomedcentral.com/articles/10.1186/1471-2369-13-164>

**Table 3: Summary of new evidence of long-term eculizumab use post-transplant (in patients commenced peri-transplant)**

	Vande Walle 2017	Zuber 2017	Levi 2017	Case reports
Design	Registry data (conference presentation slides)	Case series, multi-centre retrospective (conference abstract)	Case series	Case reports: de Andrade 2017, Brocklebank 2017
N	144	95	12	3 <sup>g</sup>
Number treated with ecu. peri-transplant	67. Of these, 51 were maintained on "approved ecu. dosing"	35	10	3
Risk of subsequent TMA	NR	NR	Medium-high risk	NR
Duration of eculizumab	>12 months in the 51 patients maintained on approved ecu.dosing	NR No information re. duration / discontinuation of ecu.	1 discontinuation after 28.7 months.	Unclear (4 to 16 months)
<b>Outcomes</b>				
Subsequent TMA	NR	0% at 12 months	0% <sup>b</sup>	25% <sup>f</sup>
Graft Survival	NR	100% at 12 months	100% <sup>b</sup>	75% <sup>f</sup>
Patient Survival	No deaths reported	No deaths reported	No deaths reported	100%
Follow up	Median 2.3 years	NR	Median 21months <sup>b</sup>	9 to 16 months
Other related information	% who required dialysis post transplant: - All patients: 9% (6 of 67) - "Approved ecu dosing" group: 8% (4 of 51) <sup>a</sup>	aHUS recurred in 1 patient, 21 months after eculizumab discontinuation, leading to graft loss 4 months later <sup>d</sup> "Overt clinical recurrence" occurred in 17 cases. <sup>d</sup>	Patient who discontinued was monitored for 9 months with no recurrence. <sup>c</sup>	In de Andrade 2017, one patient had graft loss due to TMA. <sup>f</sup>

Source: Table 6, p33-35 of the resubmission; Table 7, p36 of the resubmission; Slide 9, Vande Walle 2017; pp11-12 and p28, Levi 2017; Zuber 2017; Table 2 p7, de Andrade 2017;

ecu. = eculizumab; NR = not reported; TMA = thrombotic microangiopathy

<sup>a</sup> Vande Walle, Slide 9: This is data for any new dialysis, including chronic and acute.

<sup>b</sup> In patients treated peri-transplant

<sup>c</sup> Based on text on pages 11-12 of the publication; and Table 2, page 28 of the publication

<sup>d</sup> As stated in the conference abstract publication

<sup>e</sup> The resubmission indicated that the new case reports were: de Andrade 2017, Krishnan 2017 and Brocklebank 2017. Note that Krishnan 2017 also related to discontinuation outcomes (patient discontinued after 8 months), and so is reported in Table 4 only. Brocklebank 2017 included very limited information

<sup>f</sup> de Andrade 2017 included two patients who were treated prophylactically with eculizumab. Both were on chronic eculizumab treatment: one patient experienced relapsed TMA after 4 months; the other patient remained asymptomatic after 16 months of follow-up.

6.11 A total of 115 patients, who received eculizumab peri-transplant then continued eculizumab therapy post-transplant were reported in the resubmission. Limited information were available about the duration of use of eculizumab and patient outcomes. The resubmission did not present aggregated outcomes from these data.

#### Registry data (Vande Walle 2017)

6.12 Updated data were presented from the Global aHUS registry (Vande Walle 2017), with a data-cut date of August 2016. These were conference presentation slides, which the resubmission stated were presented at the European Renal Association congress in May 2017. Limited information from the same data-cut had been outlined in the July 2017 Pre-PBAC response, based on the conference abstract (rather than the conference slides). This represented further information, and

potentially a later data-cut, than the registry data presented in the July 2017 submission (a conference abstract by Siedlecki 2016).

- 6.13 Vande Walle 2017 included registry patients with a kidney transplant who were treated with eculizumab and had at least one year of follow-up after their most recent transplant. The aim of the analysis was to assess the incidence of dialysis post-kidney transplant in patients who initiated eculizumab pre-transplant, versus those who initiated post-transplant.
- 6.14 The analysis also assessed the incidence of dialysis in patients who were maintained on “approved eculizumab dosing” versus “all patients” (including those who discontinued eculizumab). As shown on Slide 9 of Vande Walle 2017:
- Of patients who started eculizumab pre-transplant, patients receiving “approved eculizumab dosing” had a lower incidence of chronic dialysis than “all patients” combined (incidence rate: 0.7 per 100 patient years versus 1.6 per 100 patient years, respectively). However, of the 3 patients who required acute dialysis, all were in the “approved eculizumab dosing” group.
  - The analysis included 16 patients who were not maintained on “approved eculizumab dosing”. Dialysis (chronic or acute) was required for two of these 16 patients (based on data for all patients minus the patients maintained on approved eculizumab dosing; the incident rate per 100 patient-years was not reported for this group separately), compared with four of the 51 patients maintained on approved eculizumab dosing (incident rate per 100 patient-years: 2.7 (95% CI: 1.5 - 8.9)). Overall, limited data were available; the duration, dosing and reasons for not adhering to approved eculizumab dosing were not known.

#### Legendre 2017

- 6.15 Legendre 2017 was a pooled post hoc analysis of the four prospective clinical trials (C08-002, C08-003, C10-003 and C10-004) which were presented in the March 2014 submission and other subsequent submissions. The resubmission reported the median duration of treatment with eculizumab in these trials, but did not report any outcomes from these data.
- 6.16 Overall, the studies included 26 patients who had received a kidney transplant. However, Figure 2 of the publication indicated that not all patients commenced eculizumab peri-transplant. Further, the duration of eculizumab therapy in relation to outcomes was not reported. Thus this data may have limited applicability to the proposed treatment setting.

#### **ii) Patients who discontinued eculizumab post-transplant**

- 6.17 The resubmission outlined eight cases (all from case studies) in which patients discontinued eculizumab post-transplant (having commenced eculizumab peri-transplant), two of which were new: Krishnan 2017 and Levi 2017. The outcomes are summarised in the table below, with the previously seen studies shaded grey. The

reasons for discontinuation were not known in most cases. The resubmission stated that there were a high proportion of donations from living donors, which tend to be associated with superior outcomes.

**Table 4: Summary of evidence without sustained long-term eculizumab post-transplant (in patients commenced peri-transplant)**

	n	mutation	Graft donor	Duration of ecu post-transplant	Reason for discontinuing	Outcome
Krishnan 2017	1	CFH	Living	8 months	Pt choice	Graft deterioration 5 months after ecu was ceased. Re-initiated ecu. Serum creatinine returned to baseline one month post re-initiation of ecu.
Levi 2017	1	Unknown	Deceased	29 months <sup>a</sup>	NR	No signs of TMA after 9 months.
Ardissino 2016	1	Anti-CFH antibody	NR	5.5 months	Antibody no longer detected	Satisfactory graft function at 52 months follow-up
Coppo 2015	1	CFH	Deceased	42 months <sup>a</sup>	NR	No TMA after 5 months follow-up. Pt. received a subsequent liver transplant
Matar 2014	3	No known	Living	6 months each	NR	Functioning graft reported at 21, 26 and 34 months.
Kasapoglu 2015	1	CFH	Living	5 weeks	NR	No TMA or graft dysfunction reported at 12 months follow-up

Source: text pp17-18 of the resubmission; Grey = studies that were previously seen

CFH = complement factor H; ecu = eculizumab; NR = not reported; pt = patient; TMA = thrombotic microangiopathy

<sup>a</sup> Unclear if all eculizumab therapy was post-transplant; Follow-up timeframes were unclear

6.18 A total of eight cases of patients who discontinued eculizumab post-transplant were reported. No graft loss was reported in any of the patients. There was only one report of aHUS recurrence, which occurred five months after eculizumab was ceased (Krishnan 2017). The patient recommenced PBS-subsidised eculizumab with immediate improvement in graft function. His creatinine returned to baseline within one month of the re-introduction of eculizumab.

6.19 The registry data reported in Vande Walle 2017 also included outcomes (incidence of dialysis) for patients who were not maintained on “approved eculizumab dosing”, as outlined above.

### iii) Comparator studies: Historical outcomes prior to eculizumab availability

6.20 The resubmission presented data to demonstrate the natural history of patients with aHUS who underwent renal transplantation prior to eculizumab being available. Table 5 outlines data from publications that have not previously been presented to the PBAC. The resubmission stated that duplication of patients across publications was inevitable.

**Table 5: Historical data: subsequent TMA and graft loss in patients at medium-high risk of subsequent TMA prior to the availability of eculizumab - new publications**

	Population	Number of patients	Number of transplants	Subsequent TMA	TMA resulting in graft loss	Overall Graft Loss	Graft loss due to TMA
Bresin 2006	CFH & CFI mutations	30	39	24/39 (62%) <sup>a</sup>	NR	29/39 (74%)	24/27 (89%) <sup>b</sup>
Noris 2013	Multiple mutations <sup>c</sup>	117	154	94/154 (61%)	79/94 (84%)	NR	NR

Source: Table 1, p11 of the resubmission

CFH = complement factor H; NR = not reported; TMA = thrombotic microangiopathy

<sup>a</sup> Subsequent TMA was only recorded where it was the cause of overall graft loss. There may have been other patients who experienced TMA which didn't result in graft failure. This figure may therefore be an under-representation of the number of patients experiencing TMA

<sup>b</sup> Cause of graft loss was not reported in two patients

<sup>c</sup> Mutations included were: CFH, CFH/CFHR1 hybrid, CFI, C3, CFB, CFH-Ab.

6.21 The resubmission stated that these data demonstrate that patients with aHUS who undergo renal transplantation have a high risk of developing subsequent TMA. However, these data do not reflect current treatment options in Australian clinical practice. For example it did not incorporate eculizumab (3 months post-transplant, with re-initiation upon recurrence of aHUS) or prophylactic plasma exchange/infusion.

### iii.a) Complement amplifying conditions

6.22 The resubmission argued that complement amplifying conditions that may present beyond three months post-transplant include pregnancy, malignant hypertension, autoimmune diseases, infections and surgery, along with immune response to allograft endothelium, related infections, ischaemia reperfusion lesions, rejection and medicines used to enable transplant. The resubmission stated that these factors made recurrence of TMA "highly probable".

### iv) Inpatient funding of eculizumab

6.23 The resubmission did not present any new evidence to support its request for inpatient funding of eculizumab. The resubmission re-iterated arguments provided in its July 2017 Pre-PBAC response and stated that without PBS-subsidised inpatient access, "funding decisions would be made at the discretion of individual hospitals and state health services" which could "introduce delays to therapy and potentially delay transplant".

### Comparative harms

6.24 The resubmission did not present any data relating to the safety or comparative safety of eculizumab.

6.25 In its March 2014 consideration, the PBAC noted that the comparative safety of long-term eculizumab is still to be determined. Further, the PBAC noted that the safety of the long-term use of eculizumab in patients with complete remission of aHUS and renal function is also not known (Eculizumab PSD, March 2014 PBAC Meeting). The

PBAC re-iterated this in July 2017, as no data were submitted to address this issue at that time (July 2017 PBAC Public Summary Document, para 6.45).

- 6.26 The pre-PBAC response stated the eculizumab Periodic Safety Update Report found that the rate of meningococcal infections was 0.31 per 100-patient-years across all indications, and 0.28 per 100 patient-years in patients with aHUS (for the period October 2016 to October 2017). The pre-PBAC response stated this was similar to the rates reported previously. Fatal outcomes in patients experiencing meningococcal infection occurred at a rate of 0.03 per 100 patient-years.

### **Interpretation of clinical evidence**

- 6.27 The implied clinical claim in the resubmission was that 12 months of prophylactic eculizumab therapy post-transplant was superior to three months of eculizumab therapy followed by monitoring for recurrence of aHUS in patients receiving a renal transplant. The Pre-PBAC response confirmed that this was the intended clinical claim.
- 6.28 In its July 2017 consideration, the PBAC considered that there was “insufficient evidence to quantify the comparative benefits and harms of long-term prophylactic eculizumab therapy, compared to discontinuation of therapy with monitoring for recurrence of TMA, in patients in complete remission post-transplantation.” (July 2017 PBAC Public Summary Document, para 6.47)
- 6.29 The PBAC considered that the claim of superior comparative effectiveness and safety was not adequately supported by the data. The PBAC confirmed its July 2017 consideration as presented in paragraph 6.28 above.

### **Economic analysis**

- 6.30 The minor resubmission did not present an economic analysis.

#### **Drug cost/patient/year:**

- 6.31 For an adult patient weighing at least 40kg (assumes inpatient and ongoing maintenance treatment):
- Initial phase: 900mg weekly x 4, \$71,250/patient (public);
  - Initial phase with additional dose at graft reperfusion: \$89,063/patient (public);
  - Maintenance phase: \$617,500/patient/year (public) (assuming 1200 mg every 2 weeks = 4 vials x (52 weeks ÷ 2) = 104 vials per year).
- 6.32 Based on the recommendation provided by the PBAC in July 2017 the cost per course would be \$118,750/patient (public). This assumes 1200 mg every 2 weeks = 4 vials x (10 weeks ÷ 2) = 20 vials per treatment course.

### Estimated PBS usage & financial implications

- 6.33 The resubmission stated that no changes were made to the patient estimates compared with the previous submission. As a minor resubmission, the financial estimates were not fully evaluated. However, during preparation of the minor overview, a number of changes to the financial estimates were noted.
- 6.34 Firstly, the financial estimates assumed patients would receive one full year of eculizumab therapy under this restriction.
- The July 2017 submission had assumed all patients initiated on eculizumab in this setting would continue for the for the full five year forward estimates period (i.e. patients initiated in Year 1 would still be treated in Year 5); this assumption had substantially contributed to the estimated financial impact in the previous submission.
- 6.35 Secondly, the estimated number of vials per patient increased because the current resubmission used the full adult dose (rather than weighted average dosing in the previous submission). That is:
- the July 2017 submission assumed that patients would receive an average of less than 10,000 vials per full year of treatment. This was lower than the maintenance dose stated in the Product Information, which is 104 vials for patients  $\geq 18$  years of age or  $\geq 40$  kg. The July 2017 Pre-PBAC response clarified that fewer vials were assumed because weighted average dosing was assumed (e.g. including children and adolescents) as opposed to the full adult dosing. Further, the July 2017 Pre-PBAC response acknowledged that if the adult dose were used for all patients, then the financial estimates would be exceeded, but proposed an expenditure cap in line with the "original estimates" (i.e. based on 88 vials per patient) stating that the sponsor would "assume the risk of any potential PBS budget over-expenditure due to uncertainties in dosing regimens...". (July 2017 Pre-PBAC Response).
  - the current resubmission assumed each patient would receive less than 10,000 vials over 12 months of therapy, thus assuming all patients would receive the full adult dose. [REDACTED]

**Table 6. Estimated number of patients likely to be treated and total cost per year of the PBS in the renal transplant setting over 5 years**

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population: aHUS pts with ESRD eligible for renal transplantation	■	■	■	■	■
Number of deaths whilst awaiting transplant	■	■	■	■	■
Incident patient with ESRD	■	■	■	■	■
No. of patients undergoing renal transplantation per year	■	■	■	■	■
<b>No. of patients likely to be treated i.e. patients who have a medium to high risk of aHUS recurrent post renal transplantation</b>					
Initiating patients	■	■	■	■	■
Total patients treated with eculizumab	■	■	■	■	■
<b>Vials per year</b>					
Inpatient phase vials <sup>a</sup>	■	■	■	■	■
Outpatient phase vials <sup>a</sup>	■	■	■	■	■
Total vials per year	■	■	■	■	■
<b>Cost to the PBS</b>	\$■	\$■	\$■	\$■	\$■
Rebate for first 2 doses <sup>b</sup>	-\$■	-\$■	-\$■	-\$■	-\$■
<b>Net Cost to the PBS after rebates</b>	\$■	\$■	\$■	\$■	\$■
<b>July 2017 submission – restriction proposed by sponsor (assumed all patients continued for 5 years)</b>					
Initiating patients	■	■	■	■	■
Patients on maintenance	■	■	■	■	■
Total patients treated with eculizumab	■	■	■	■	■
No. vials for patients on maintenance <sup>c</sup>	■	■	■	■	■
No. vials for initiating patients <sup>c</sup>	■	■	■	■	■
Total vials per year <sup>c</sup>	■	■	■	■	■
Cost to the PBS – restriction proposed by sponsor	\$■	\$■	\$■	\$■	\$■

Source: Table 3, p24 of the resubmission, Table 10, para 6.55 of the July 2017 PBAC Public Summary Document.

<sup>a</sup> Assuming ■ vials in new patients as inpatients (Day 0 and Day 7) and ■ vials in patients on maintenance as an outpatient for 50 weeks based on the adult dose recommended in the Australian Product Information. New patients are assumed to initiate therapy mid-year so these patients receive one-half of a full year of maintenance vials. Estimates do not include the discretionary use of an additional 900 mg dose following graft reperfusion. Overall, the estimates comprised: ■ vials in the inpatient setting; ■ vials in the first-year (assuming initiation of therapy mid-year); and ■ vials in the subsequent year.

<sup>b</sup> The rebate would only apply to patients who receive 12 months of eculizumab therapy as proposed in the resubmission, or 6 months as proposed in the pre-PBAC response..

<sup>c</sup> Assuming ■ vials in new patients and ■ vials in patients on maintenance. New patients were assumed to initiate therapy mid-year so these patients receive one-half of a full year of maintenance vials. Estimates do not include the discretionary use of an additional 900 mg dose following graft reperfusion.

The redacted tablet shows that at year 5, the estimated number of patients was less than 10,000 per year, the estimated number of vials was less than 10,000 per year, and the net cost to the PBS would be less than \$10 million per year.

- 6.36 The resubmission estimated that the cost to the PBS, for the proposed listing, would be \$10 - \$20 million over 5 years, or \$10 - \$20 million with the RSA proposed (discussed below).

- 6.37 In July 2017, the PBAC considered that the financial estimates that were presented were not informative because, among other matters, they included low patient uptake (July 2017 PBAC Public Summary Document, para 6.56). In particular, the PBAC considered that the prevalent pool of all patients with ESRD was more representative of the probable uptake within the first few years of listing (July 2017 PBAC PSD, para 6.53).
- 6.38 The PBAC noted that if eculizumab were listed per the committee's July 2017 recommendation (ten weeks treatment to be PBS-subsidised) the cost to the PBS would be significantly less than the resubmission's proposed cost of \$10 - \$20 million over 5 years.

### Risk Sharing Arrangements

- 6.39 The resubmission proposed a revised RSA based on:
- An annual subsidisation cap, based on the estimates outlined in Table 6. The sponsor proposed that it would rebate the Commonwealth for [REDACTED]. The resubmission stated that the sponsor would assume the risk of any potential PBS over-expenditure due to uncertainties in dosing regimens or patient number estimates.
  - The rebate would be for [REDACTED] in the transplant setting which the sponsor stated would effectively rebate [REDACTED]. The rebate for [REDACTED].
- 6.40 Some patients [REDACTED].
- 6.41 [REDACTED] inpatient treatment would be 900 mg of eculizumab on Day 0 and Day 7, totalling six vials (based on the adult dose). This did not include an additional dose at graft reperfusion. Further, some patients may require a longer hospitalisation; [REDACTED].
- 6.42 The pre-PBAC response claimed that the average length of stay for renal transplant recipients is 10.9 days and that Australian renal transplant physicians have advised that the average length of stay may currently be closer to five days. The pre-PBAC response claimed this would mean that the second dose (at Day 7) would be given as an out-patient.
- 6.43 As noted in the financial estimates above, the RSA proposed [REDACTED] (which substantially increased the cost per patient per year); and [REDACTED].

RSA in other treatment settings

- 6.44 In its July 2017 consideration, the PBAC had recommended that the Department should negotiate with the Sponsor to establish a RSA for the current listing for active TMA in patients with aHUS. (July 2017 PBAC Public Summary Document, para 7.7)
- 6.45 The resubmission stated that an RSA proposal had been submitted to the Department.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend increasing the treatment duration of PBS-subsidised eculizumab for prophylactic use in patients with end stage renal disease due to aHUS in the renal transplant period. The evidence presented to support the longer duration of treatment than previously recommended by the PBAC did not reliably address the key issues, and did not prove substantial incremental benefit. As such, the PBAC re-affirmed its July 2017 recommendation that eculizumab should be available for a maximum duration of three months in this setting (ten weeks of which would be PBS-subsidised).
- 7.2 The PBAC noted that the clinical claim proposed was that 12 months of prophylactic eculizumab post-transplant was superior to three months of eculizumab followed by monitoring for recurrence of aHUS in patients receiving a renal transplant.
- 7.3 The PBAC noted that no direct comparative data were presented to support this claim. The PBAC considered that the data that had been presented for sustained use of eculizumab post-transplant and for historical outcomes (pre-eculizumab), comprising case series and registry data, were not reliable (e.g. the data were confounded, there was heterogeneity between data sources and limited information was available about the duration of eculizumab therapy and patient outcomes).
- 7.4 The PBAC re-affirmed its previous recommendation that eculizumab should be available in this setting for a maximum duration of three months, and that in-patient treatment should not be subsidised by the PBS. The PBAC noted that patients with recurrence of aHUS after this time would be eligible for eculizumab under the current listing ('rescue therapy').
- 7.5 The PBAC considered that rescue therapy alone would be sufficient for many patients, and that three months of prophylactic eculizumab could represent over-treatment for some patients. In forming this view, the PBAC considered:
- a Dutch case series of 17 patients at high/medium risk of recurrence who did not receive prophylactic eculizumab. Of these, only one patient had a recurrence of aHUS and this was successfully treated with eculizumab. The

PBAC noted that all patients in the case series underwent living donor transplant and were therefore at a lower risk of recurrence than some patients in Australian clinical practice. Nevertheless, the PBAC considered that this study suggested that the risk of aHUS recurrence may be lower than previously reported and that eculizumab rescue therapy alone may be adequate for many patients.

- data from the Australia and New Zealand Dialysis and Transplant Registry that showed that clinicians perform renal transplants on patients with HUS, despite eculizumab not being available for prophylactic use post-transplantation. The PBAC further noted that deceased donor transplants are common in patients with HUS, despite being associated with a higher risk of recurrence. The PBAC considered that this further indicated that clinicians are not necessarily withholding transplantation for fear of recurrence leading to graft failure (in the knowledge that eculizumab was available should recurrence occur).
- 7.6 The PBAC noted that the cost to the PBS for treating less than 10,000 patients (as estimated by the resubmission) would increase to \$10 - \$20 million over five years if the duration of eculizumab therapy were increased from three months as previously recommended, to 12 months as proposed in the resubmission.
- 7.7 The PBAC re-iterated its previous concerns that the financial estimates were not informative because, among other matters, patient numbers were underestimated.
- 7.8 The PBAC re-iterated its previous recommendation that a Risk Sharing Arrangement with a hard cap would be appropriate for this setting.
- 7.9 The PBAC also re-iterated its previous recommendation that the Department should negotiate with the Sponsor to establish a Risk Sharing Arrangement for the current listing for active TMA in patients with aHUS.
- 7.10 The PBAC recalled the broader context for the current PBS-listing of eculizumab for the treatment of active TMA in patients with aHUS. The PBAC recalled that, in December 2015, the data available showed that eculizumab led to improvements in the first 12 months of therapy but did not show a consistent improvement across all parameters in the 12 to 24 month period. The PBAC further recalled that its December 2015 recommendation to increase the duration of eculizumab therapy from 12 to 24 months was for the purpose of enabling a review of additional evidence when available. The PBAC recommended that as additional data are now available, a review is warranted into the question of whether there is incremental effectiveness and safety from 24 months or longer of eculizumab therapy compared with 12 months or shorter (that is 3 or 6 months) of eculizumab therapy for the first treatment of active TMA in patients with aHUS. The PBAC requested that an evaluation of the published and local evidence be undertaken, with input from the Eculizumab Reference Group.

- 7.11 The PBAC noted that this resubmission is not eligible for an Independent Review as Independent Review is not available in response to a request to modify or extend an existing listing.

**Outcome:**

Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

Alexion is disappointed that the PBAC has not modified the previous recommendation to treat patients with aHUS undergoing renal transplant for longer than 3 months with Soliris (eculizumab). Alexion is, however, committed to ensuring that patients with aHUS who require Soliris to facilitate a renal transplant, now receive rapid access to therapy, and have the ability to access therapy again should TMA represent in the graft. As such Alexion look forward to working with the Department of Health and Government to ensure an expedited review of the risk sharing agreements proposed by Alexion and to ensure urgent funded access to Soliris for patients with aHUS to facilitate renal transplantation.