4.01 ECULIZUMAB
Solution concentrate for I.V. infusion 300 mg in 30 mL, Soliris®, Alexion Pharmaceutical Australia Pty Ltd.

1 Purpose of Application

1.1 The minor resubmission requested an extension of the current Authority Required Section 100 (Highly Specialised Drugs Program) listing for eculizumab for the treatment of 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 submission requested access to eculizumab treatment for 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 current requirement for evidence of active, progressive TMA, to prevent recurrence of TMA and graft loss.

2.2 The sponsor requested initiation of eculizumab at the time of renal transplantation (peri-transplantation), and sustained access to eculizumab post-transplantation to protect the renal allograft. In its March 2016 consideration of the use of eculizumab in patients undergoing renal transplantation, the PBAC considered *"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 web outcome).*

2.3 The submission continues to assume PBS subsidised treatment will 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.

2.4 Under the current PBS listing, aHUS patients with either their native kidneys or a renal allograft are eligible to receive eculizumab if they have evidence of active,

progressive TMA and they meet the other restriction criteria.

2.5 The submission requested a number of changes to the existing restrictions to accommodate the new patients eligible for treatment.

2.6 The PBAC considered that a separate restriction for this indication was required for administrative simplicity and to remove internal inconsistencies such as the patient must not have reached end stage renal disease. The finalised restriction can be seen in paragraph 8.1 below.

2.7 The PBAC also considered that prescribers should be restricted to nephrologists or paediatric nephrologists within a transplant unit.

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

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 fourth submission for eculizumab to the PBAC for the treatment of aHUS.

3.3 The first submission was considered by PBAC in March 2013. The PBAC rejected eculizumab for PBS listing under Section 100 due to uncertainty regarding the clinical effectiveness and unacceptable cost-effectiveness of treating newly diagnosed and long-term aHUS, and patients with renal transplant (Eculizumab Public Summary Document (PSD), March 2013 PBAC meeting).

3.4 A re-submission was considered by PBAC in March 2014. The PBAC recommended the listing of eculizumab under Section 100. The PBAC was satisfied that eculizumab provides, for some patients, a significant improvement in efficacy over supportive care. This included patients with active, progressive TMA during acute episodes of aHUS who have not progressed to ESRD; and prevalent patients on long-term dialysis who have extra-renal TMA. The PBAC was unable to determine the effectiveness of eculizumab in patients on long-term dialysis. The PBAC noted the significant morbidity and mortality associated with long-term dialysis for patients who do progress to ESRD. However, the PBAC considered that it was important that further information is obtained regarding the risk-benefit profile of long-term eculizumab, and how this differs between patient groups (Eculizumab PSD, March 2014 PBAC meeting).

3.5 The previous March 2016 minor submission, to extend the current listing for eculizumab to include patients who had progressed to ESRD and were scheduled to receive a renal transplant, was submitted following a request from the PBAC for a summary of relevant data that had become available since the PBAC's consideration of eculizumab in March 2014 - on the use of eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) following kidney transplantation. This matter was discussed at the stakeholder meeting held on 24 June 2014, with the meeting record stating that:
"Although the significant morbidity and mortality associated with long-term dialysis for patients who had progressed to end stage renal failure was noted by the PBAC in March 2014, the Committee was unable to determine the efficacy and cost-effectiveness of eculizumab for prevention of recurrence of thrombotic microangiopathy (TMA) following kidney transplantation. Data about use in these patients should become available over time and therefore, this additional indication could be reconsidered for subsidy in the future." New evidence presented in the March 2016 submission included two case series (N=[redacted]) and [redacted] case reports.

3.6 The PBAC rejected the March 2016 submission on the basis that the submission provided sparse data in support of the use of eculizumab in a renal transplant setting. No comparative data were available to determine the relative effectiveness of eculizumab compared with supportive care.

3.7 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 the utilisation of eculizumab was inconsistent with the intent of the Committee's recommendations for the drug. The PBAC considered that observed patterns in the first 12 months of PBS listing for eculizumab raised questions about the accuracy of the estimates presented to the Committee in the sponsor's submissions, and about the reliability of information provided in prescribers' applications for PBS-subsidised eculizumab, and
- that the larger than expected number of patients ([redacted] vs [redacted]) 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.

3.8 The PBAC also considered that 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.

3.9 The PBAC recommended that the Department engage with the sponsor of eculizumab to negotiate an appropriate arrangement to manage the risks indicated in the first 12 months' utilisation data. The Committee advised it would be appropriate for the Department to enter into a Risk Sharing Arrangement with the sponsor where financial caps would limit cost to Government to appropriate use under the PBS listing for aHUS, with the sponsor to rebate the cost of any utilisation above the financial cap. Discussions between the Department and the sponsor regarding this risk share are continuing.

3.10 The current minor resubmission presents new data from the Global aHUS Registry, four retrospective case series studies and 4 case reports. A summary of changes made between the March 2016 submission and the current re-submission is presented in Table 1.

Table 1: Comparison table between March 2016 submission and the July 2017 resubmission.

	March 2016 submission	Current resubmission
Requested PBS listing	To request access to eculizumab treatment for two subgroups of patient with aHUS in the renal transplant setting, to prevent recurrence of thrombotic microangiopathy (TMA): 1) Patients with end stage renal disease (ESRD) on chronic dialysis who are suitable for renal transplantation, without the current requirement for evidence of active, progressive TMA; and 2) Patients who have been deemed a "treatment failure" under the current criteria PBS but who have access to a renal allograft.	To request access to eculizumab for patients with a diagnosis of aHUS in end stage renal disease (ESRD) on chronic dialysis who are suitable for renal transplantation, and have a medium to high risk of subsequent TMA, without the current requirement for evidence of active, progressive TMA. *Although the submission no longer specifically requests a listing in patients who have previously failed eculizumab but have access to a renal allograft, the requested restriction also does not exclude these patients.*
Requested effective DPMQs	• $5937.50 (Public) • $5984.52 (Private)	• Same as previous.
Comparator	No comparator nominated by Sponsor. **PBAC:** Suggested that supportive care, consisting of long-term dialysis or renal transplantation with prophylactic plasma exchange/infusion, was an appropriate comparator (paragraph 5.2).	• Sponsor claimed 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.

	March 2016 submission	Current resubmission
Clinical evidence	• Previously assessed for original listing: •One retrospective case series evaluating eculizumab for the prevention or treatment of aHUS recurrence after renal transplantation (reported in both Zuber 2012 and Noris 2013); •Post-hoc subgroup analyses from three prospective, open-label, single-arm studies of eculizumab for aHUS (Studies C08-002, C08-003 and C10-004); •An analysis of pooled data from patients in Studies C08-002, C08-003, C10-003 and C10-004 (Legendre 2015); •4 case reports detailing interrupted eculizumab dosing in patients with aHUS and a transplanted kidney. New studies: •Two retrospective case series evaluating eculizumab for prevention or treatment of aHUS recurrence after renal transplantation (Matar 2014 and Sheerin 2015); •14 case reports describing the use of eculizumab to prevent TMA recurrence in aHUS patients undergoing renal transplantation, including one patient who had previously failed treatment with eculizumab. One additional case report was identified during the evaluation; and •5 case reports detailing interrupted eculizumab dosing in patients with aHUS and a transplanted kidney. Two of these case reports were excluded from the evaluation.	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.
Key effectiveness data	Post transplant Graft function satisfactory: 32/34 (94%). Re-occurrence of TMA: 1/9 (11.1%) only one study reported. **PBAC comment**: (paragraph 7.2 and 7.3) No comparative data were available to determine the relative effectiveness of eculizumab compared with supportive care. However, the PBAC also considered that the clinical data provided did not permit a confident estimate of the magnitude of the additional benefit over supportive care (ongoing dialysis), prophylactic use versus treatment should recurrence occur, and long-term use versus short term use	A total of 147 patients have been reported in the newly submitted, published literature as receiving prophylactic treatment with eculizumab, initiated peri-transplant. *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%.*

	March 2016 submission	Current resubmission
Clinical claim	Eculizumab is effective in preventing post-transplantation recurrence of TMA and graft loss. **PBAC comment**: (paragraph 6.51) The PBAC considered that while the claim that eculizumab is effective in preventing post-transplantation recurrence of TMA and graft loss was reasonable, it was not possible to confidently quantify the extent of the clinical benefit.	Not explicitly stated, assumed to be the same as previous.
Economic evaluation	None presented.	Same as previous.
Number of patients	[redacted] per year. **PBAC comment**: (paragraph 7.6) The PBAC considered that, in light of the natural history and prognosis of atypical HUS, it would be reasonable to conclude that most or all HUS cases leading to ESRD would be the atypical form of the disease. The PBAC therefore did not consider that the submission's estimate of [redacted] additional patients per year was reasonable or adequately justified	[redacted] patient in the first year decreasing to [redacted] per year from year 3: Applying a transplantation rate of 22.7% to the known [redacted] patients awaiting transplantation, results in [redacted] patients potentially receiving a transplant with prophylactic eculizumab in year 1 of listing.
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 (Based off updated patient numbers and assuming continued treatment). **PBAC comment**: (paragraphs 7.9) The PBAC requested that the Department engage with clinical stakeholders to clarify the likely number of patients who would use eculizumab in a renal transplant setting, and to determine the most appropriate duration of treatment following transplant.	Less than $10million 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).
Risk sharing arrangement	None proposed. PBAC comment: (paragraph 6.64) The PBAC advised that in light of the observed utilisation, a risk share agreement for the current listing, based on the patient numbers from the March 2014 submission, would appropriately contain the financial risk to the Commonwealth.	Same as previous.

	March 2016 submission	Current resubmission
PBAC decision	Reject **PBAC Comment:** (paragraph 7.1 and 7.2) The PBAC rejected the submission to extend the current listing for eculizumab for atypical haemolytic uraemic syndrome (aHUS) to include use in a renal transplant setting. The PBAC noted that the submission provided sparse data in support of the use of eculizumab in a renal transplant setting. No comparative data were available to determine the relative effectiveness of eculizumab compared with supportive care.	-

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

4 Clinical place for the proposed therapy

4.1 aHUS is a rare, life-threatening genetic disease characterised by microangiopathic haemolysis, thrombocytopenia, and organ damage. aHUS is caused by a genetic inability to regulate complement; however, up to 50% of patients with aHUS do not yet have an identified genetic mutation. Patients who survive the presenting manifestations are burdened with a chronic thrombotic and pro-inflammatory state which carries a life-long elevated risk of renal failure and other severe complications. Renal transplantation is problematic for patients with aHUS and ESRD due to the high proportion of transplanted patients who experience subsequent recurrent aHUS with TMA in the transplanted organ and a high risk of graft failure.

4.2 The PBAC previously considered aHUS to be a severe disease, associated with high risk of end stage renal failure and mortality, particularly at its first presentation. The PBAC considered that there is a high clinical need for an effective treatment for aHUS, particularly acute events. The PBAC also noted the significant morbidity and mortality associated with long-tern dialysis for patients who progress to ESRD (Eculizumab PSD, March 2014 PBAC meeting).

4.3 The PBAC has considered aHUS to be a heterogeneous disease with a wide variation in its natural history and how it responds to treatment. The natural history of aHUS is influenced by factors such as the patient's genetic sub-type, environmental triggers and the stage of disease. The PBAC considered that understanding of the role of these factors, and their impact on disease severity, risk of recurrence, prognosis, or the best treatment option for a patient is currently evolving (Eculizumab PSD, March 2014 PBAC meeting).

4.4 The current submission proposes that all aHUS patients undergoing renal transplantation with a medium to high risk of subsequent TMA in the allograft receive prophylactic eculizumab initiated at the time of transplantation and sustained after kidney transplantation.

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

5 Comparator

5.1 The submission stated that there were currently no other TGA approved, nor PBS funded treatments for aHUS.

5.2 However, consistent with the advice from the PBAC, the submission provided

literature based comparisons with long-term dialysis, renal transplantation with prophylactic plasma exchange/infusion and treatment initiation at recurrence of active TMA post-transplantation.

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

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (226), health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with eculizumab in the proposed setting including allograft survival, better quality of life, and the chance to cease dialysis along with the possibility of a return to work.

6.3 The PBAC noted the support received from Kidney Health Australia to allow for equitable access to kidney transplantation for patients with aHUS and to ensure post-transplant outcomes are optimised.

Clinical trials

6.4 The committee recalled the agreed outcomes of the February 2016 clinical advice meeting on eculizumab in the context of renal transplant, as summarised from the Clinical advice meeting statement (February 2016)below.

Clinical advice meeting

6.5 A clinical advice meeting was held on 12 February 2016 to discuss the place of eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) in the context of renal transplantation. All invited clinicians participated, including the Chair and members of the Pharmaceutical Benefits Advisory Committee (PBAC), and clinicians with expertise in the fields of nephrology, haematology and organ transplantation.

Risk of onset of aHUS post transplantation

6.6 Some assessment of risk of aHUS post transplantation is possible, although definitive characterisation of an individual's level of risk is difficult. Clinical assessments in Australian practice are based on identifiable genetic mutations and the patient's prior history of graft loss due to aHUS.

Genetic basis

6.7 The genetic basis for aHUS is not yet fully understood and given the rarity of the disease data are relatively sparse. Identified mutations can be assigned high, medium or low risk, and these categorisations are likely to evolve as more data are accumulated. With current genotype-phenotype data, approximately half of Australian aHUS patients have an identified mutation, although this is proportion is likely to increase as new mutations are identified. Almost all known genotypes have a medium-high risk of recurrence of aHUS.

Previous episode of aHUS leading to loss of graft

6.8 Patients who have lost a graft due a recurrence of aHUS would be considered to be at high risk of further recurrence following a subsequent renal transplant.

Management of aHUS in the context of renal transplant

Peri-transplant dosing of eculizumab

6.9 It was considered by the clinicians that eculizumab would be appropriately required to prevent TMA in a peri-transplant setting in recipients at high risk of recurrence of aHUS. As some assessment of risk of aHUS onset is possible based on identified genetic mutations, clinicians would likely opt to give eculizumab to patients with high- or medium-risk mutations. Patients with no identified mutation would likely be treated as medium risk, and would be offered eculizumab. As patients with low-risk mutations would likely represent no more than 5% to 10% of the aHUS population, it was considered likely that most patients at risk of recurrence would receive eculizumab in a peri-transplant setting.

6.10 Eculizumab would be administered prophylactically in a single dose of 900mg prior to the start of surgery. Although for live donor transplants the timing of the surgery is more predictable than for deceased donor transplants, it was noted that in either case the dose would likely be administered within 24 hours of the procedure.

Ongoing eculizumab following renal transplantation

6.11 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).

6.12 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.

6.13 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.

6.14 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.

6.15 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.

6.16 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.

Access to eculizumab for patients previously deemed to have failed to respond to eculizumab

6.17 It was noted that some patients may receive eculizumab under the current listing, fail to respond to treatment and progress to ESRD and then become a candidate for renal transplant. The current listing for eculizumab defines a treatment failure as a case in which the patient is:

(1) dialysis-dependent at the time of application and has failed to demonstrate significant resolution of extra-renal complications if originally presented; or

(2) on dialysis and has been on dialysis for 4 months of the previous 6 months while receiving PBS-subsidised eculizumab and has failed to demonstrate significant resolution of extra-renal complications if originally presented.

6.18 These criteria, among others, are applied once a patient has received 24 weeks of treatment with eculizumab. It was asked whether a patient's condition would respond to eculizumab following renal transplant when 24 weeks of treatment had not adequately controlled the condition previously.

6.19 It was noted that there is a lack of high quality data to predict a patient's response to eculizumab under these circumstances. It was speculated that, as dialysis can stimulate complement activity, this may complicate a prediction of such a patient's response to subsequent treatment. It was noted that an assessment of any extra-renal manifestations of aHUS would provide context to determine the previous response to treatment and possible future response.

Treatment setting

6.20 With regard to current Australian practice, it was noted that the majority of aHUS patients are treated in public hospital settings, predominantly by specialists in nephrology and haematology.

6.21 It was noted that the United Kingdom initially established a specialised centre to co-ordinate management of aHUS treatment with eculizumab. Under such a model, while not all patients would travel to the centre for management of their condition, the centre would take on an oversight and co-ordination role. The merits of this approach were noted, in that it would promote consistent care of all aHUS patients across the country and would provide additional opportunities to enhance data capture.

Data capture

6.22 It was also noted that the quality of data submitted by prescribers in support of applications for continuing treatment was variable. Of particular note was that genetic testing of aHUS patients did not appear to be a universal approach among clinicians. While the time impost of reporting for clinicians was noted, this needs to be considered in the context of the very substantial societal cost incurred subsidising the drug.

6.23 While it is likely that genotyping is increasingly performed it is not a consistent practice. It was noted that the proportion of patients without genotyping will continue to diminish. The role of PBS restrictions in driving testing practices, as it has with ADAMTS-13 for the current listing, was noted.

6.24 The possibility of improving data capture through a trial was discussed. Although PBS subsidy cannot be limited only to trial settings, improved data quality was noted as a potential benefit.

Other matters

6.25 The PBAC Chair reminded meeting attendees that the Committee has an obligation under the *National Health Act 1953* to advise the Minister for Health about the cost effectiveness of a drug. The administrative process for eculizumab was noted to be highly complicated for prescribers, patients and the Commonwealth. Although a simpler approval mechanism would be preferable, the current process attempted to balance facilitated access for patients in genuine clinical need with the extremely high price of the drug. In the absence of robust eligibility criteria and a stopping rule, eculizumab is not likely to be cost effective.

Current submission

6.26 The submission relied in part on previously submitted studies (previously presented in the March 2014 re-submission and March 2016 submission) which included, four open-label, single arm studies, five retrospective case series, and 40 case reports (3 of which detailed interrupted eculizumab dosing in patients with aHUS and a transplanted kidney).

6.27 Evidence that had not been previously assessed by the PBAC but was presented in the current submission included:

- A Global aHUS Registry data (Siedlecki et al. 2016);
- Four retrospective case series evaluating eculizumab for prevention or treatment of aHUS recurrence after renal transplantation (Ardissino et al.

2016, Kumar et al. 2016, Levi et al. 2016 and Andrade et al 2016);

- 4 unseen case reports describing the use of eculizumab to prevent TMA recurrence in aHUS patients undergoing renal transplantation including 2 cases where eculizumab treatment had been withdrawn post transplant.

6.28 The PBAC noted that while, limited details were available in the global aHUS registry data and case series as they were abstracts of papers submitted for conferences or a brief supplemental publication (Kumar et al. 2016) it was an improvement on the data submitted in support of the previous March 2016 submission. Data presented were restricted to the numbers of patients treated and outcomes with no individual patient data.

6.29 Details of the reports presented in the submission are provided in the table below.

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

Trial ID	Protocol title/ Publication title	Publication citation
Global aHUS Registry Data		
Siedlecki 2016	Siedlecki, A., Isbel, N., Van de Walle, J., Kupelian, V. & Cohen, D. J. Timing of eculizumab treatment and the need for dialysis in patients with aHUS who receive a kidney transplant.	American Society of Nephrology Kidney Week 2016 [Abstract TH-OR095]
Case series		
Ardissino 2016	Gianluigi Ardissino, Donata Cresseri, Antenore Giussani, Stefania Salardi, Francesca Tel, Sara Testa, Michela Perrone, Fabio Paglialonga, Mirco Belingheri, Martina Sgarbanti, Lucrezia Furian, Angela Nocco, Silvana Tedeschi, Piergiorgio Messa. Kidney Transplant in Atypical HUS: A Single Center Experience	American Society of Nephrology (ASN) Kidney Week SA-PO365
Kumar 2016	A. Kumar, Z. Stewart, A. Reed, D. Orozco, R. Smith, C. Nester, C. Thomas. Successful prophylactic use of eculizumab in aHUS kidney transplant patients: a report of 9 cases.	American Journal of Transplant, 16 (Suppl 3).
Levi 2015	Charlene Levi, Veronique Fremeaux-bacchi, Anne Scemla, Julien Zuber, Christophe M. Legendre, Rebecca Sberro-Soussan. Outcome after eculizumab therapy to prevent recurrence of atypical haemolytic uremic syndrome: experience in eleven renal transplant recipients.	American Society of Nephrology (ASN) Kidney Week SA-PO1082
Andrade 2016	Andrade, A. V., Machado, D., Souza, P. S., Paula, F. De & David-Neto, E. Use of eculizumab for atypical haemolytic uremic syndrome in kidney transplantation - single centre experience in Brazil.	American Society of Nephrology (ASN) Kidney Week (PUB749)
Case reports		
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
Kasapoglu 2015	Kasapoğlu, U. et al. Prophylactic Eculizumab Use in Kidney Transplantation: A Review of the Literature and Report of a Case with Atypical Haemolytic Uremic Syndrome.	Ann. Transplant. 20, 714–9
Coppo 2016	Coppo, R. et al. Liver transplantation for aHUS: still needed in the eculizumab era?	Pediatr. Nephrol. 31, 759–768
Riddell 2016	Riddell, A., Goodship, T. H. J. & Bingham, C. Prevention of recurrence of aHUS post renal trasplant with the use of higher-dose eculizumab.	Clin. Nephrol. 86, 200–202

aHUS = atypical haemolytic uraemic syndrome
Source: Compiled from information provided on pp13, 51-69 and 90-94 of the submission

6.30 The key features of the Global registry data, case series and case reports are summarised in the table below.

Table 3: Key features of the included evidence

	N	Design	Patient population	Outcomes
Siedlecki 2016	93 (147 claimed in submission)	Registry data Peri-transplant (n=57) Post-transplant (n=36)	All aHUS patients All at least 1 renal transplant	Recurrence of TMA Dialysis required Time to dialysis
Ardissino 2016	20	Case series Group A: No prophylaxis- 7/20 (35%) Group B: Plasma exchange/plasma infusion - 5/20 (25%) Group C: Eculizumab peri-transplant 14/20 (70%)	All aHUS patients Group B were treated with eculizumab once available	Recurrence of TMA (relapse rate) Graft loss
Kumar 2016	9	Case series	All aHUS patients All received peri-treatment	Recurrence of TMA Graft loss
Levi 2015	11	Case series	All aHUS patients 9/11 peri-transplant 2/11 at recurrence of TMA	Recurrence of TMA Graft loss
Andrade 2016	8	Case series	All aHUS patients 3/8 peri-transplant 3/8 at recurrence of TMA 2/8 post graft loss	Graft loss Serum creatinine eGFR
Case reports	4	Case reports 3 day – 47 months follow-up	All aHUS patients	Recurrence of TMA Graft function

aHUS = atypical haemolytic uraemic syndrome; eGFR = estimated glomerular filtration rate; TMA = thrombotic microangiopathy
Source: Compiled from information provided on pp42-69 of the submission

6.31 In place of direct head to head trials of eculizumab with the PBAC proposed comparators, the submission relied on case series, cohort and case studies with ongoing dialysis, plasma exchange/plasma infusion and treatment at recurrence of TMA post-transplant.

6.32 Details of the reports presented in the submission are provided in the table below.

Table 4: Key features of the included evidence

	N	Design	Patient population	Outcomes
i) Evidence for ongoing dialysis				
Durkan 2016	9 (14 in total)	Cohort	All aHUS patients All required dialysis All at least 1 renal transplant	Recurrence of TMA Dialysis required Time to dialysis Graft loss Death
Neuhaus 1997	7 (66 in total)	Retrospective cohort Paediatric	All aHUS patients Long term dialysis Surviving patients received renal transplant.	Death Recurrence of TMA
Besbas 2017	8 (146 in total)	Registry data	Case ESRD	Death rate Hospitalisation rate
Brunelli 2015	217 cases; 1,085 controls	Case control	All aHUS patients 9/11 peri-transplant 2/11 at recurrence of TMA	Dialysis requirement Transplant status
Sexton 2015	2,241	Retrospective HUS cohort	HUS patients vs other ESRD patients	Death
Case reports	2	Case reports paediatric	aHUS patients Ongoing dialysis One treated with eculizumab after 7 years dialysis	Recurrence of TMA Requirement for dialysis
ii) Evidence for plasma exchange/plasma infusion				
Le Quintrec 2013	9 (57 in total)	Retrospective cohort	All aHUS PE/PI as prophylaxis	Death Recurrence of TMA
Ardissino 2016	5 (20 in total)	Retrospective cohort	As per group B in Table 2 above	
Davin 2008	3	Case series of 3 sisters	All aHUS 2 received transplant	Graft loss Recurrence of TMA
Jalanko 2008	2	Case series of infant and aunt	Both had liver-renal transplants	Graft function
Case reports	10	Case reports	All aHUS patients All at least one renal transplant	Graft function
iii) Evidence for eculizumab treatment post transplant at TMA recurrence.				
Sheerin 2015	1 (43 in total)	Retrospective cohort	"early" post operative treatment with Ec	Graft function
Zuber 2012	7 cohort 6 Literature search	Retrospective cohort and literature search	Ec range 3 days to 5 years post transplant	Resolution of TMA Graft function
Siedlecki 2016 (as in table 2)	36 (78 claimed as relevant in submission)	Registry data Peri-transplant (n=57) Post-transplant (n=36)	All aHUS patients All at least 1 renal transplant	Recurrence of TMA Dialysis required Time to dialysis
Levi 2015 (as in table 2)	2 (11 in total)	Case series	All aHUS patients 9/11 peri-transplant 2/11 at recurrence of TMA	Recurrence of TMA Graft loss
Andrade 2016 (as in table 2)	3 (8 in total)	Case series	All aHUS patients 3/8 peri-transplant 3/8 at recurrence of TMA 2/8 post graft loss	Graft loss Serum creatinine eGFR
Case reports	6	Case reports	All aHUS patients At least 1 transplant EC range 6 days to 4 years post transplant	Recurrence of TMA Dialysis required Creatinine levels Graft function/Loss

aHUS = atypical haemolytic uraemic syndrome; ESRD – end stage renal disease; TMA = thrombotic microangiopathy, PE/PI = plasma exchange/plasma infusion, Ec = eculizumab.

Source: Compiled from information provided on pp70-89 of the submission

Comparative effectiveness

6.33 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.

i) Prophylactic peri-transplant and sustained use of eculizumab in patients undergoing renal transplantation

6.34 As noted above minimal data were available in the new studies relied on in this submission. The outcomes for use of prophylactic peri-transplant eculizumab in patients undergoing renal transplantation are summarised in Table 5.

Table 5: Summary of new data presented in the submission with prophylactic peri-transplant eculizumab treatment.

	Siedlecki 2016 Peri-transplant N=57[a]	Ardissino 2016 N=14[b]	Kumar 2016 N=9	Levi 2015 N=11	Andrade 2016 Peri-transplant N=3	Case reports N=4 (new)
Median age at transplant, years	27.6	NR	6 – 40 (range)	NR	25.2 ± 7.8	13.5 (5.3 – 33)
Family history of aHUS N (%) CFH mutation detected N (%)	18 (32%) NR	NR 12 (86%)	NR 5 (56%)	NR 7 (64%)	NR 1	2 3 (+1 liver donor)
Dialysis post transplant N (%)	2 (4%)	0	0	NR	NR	0
Duration of time to dialysis, median (range), months	15.3 (12.8 – 17.9)	NA	NA	NA	NA	NA
Duration of follow-up[c],	Up to 12 months	44 years cumulative	2.6 years (median) 2 months to 5 years	21.6 months (median) ± 19	Eculizumab treatment 19.6 months ± 9.3	1 year 1 year (only 1 month Tx with Ec) 47 months (6 months post withdrawal Ec) 24 months
Serum creatinine, mean (SD), µmol/L[d]	NR	*NR*	1.05 mg/dL (0.27 – 1.7)	135 ± 60	1.2±0.1 mg/dL	0.78±0.24 mg/dL
Recurrence of TMA in patients N	4 (7%)	0	0 (1 rejection)	2 (18%) (not treated peri-transplant)	NR	1
Duration of time to TMA, median (range), months	11.4 (4.3 – 21.5)	NA	NA	day 6 and 25	NA	1
Satisfactory allograft function at last follow-up, N (%)	NR (55 inferred from as no dialysis required)	13 (93%)	9 (100%)	11 (100%)	3 (100%)	4 (100%)
Death (all causes) N (%)	1 (2%)	NR	0	0	0	0

NA = not applicable; NR = not reported; SD = standard deviation; TMA = thrombotic microangiopathy; Ec = eculizumab

[a] Numbers reported as per the provided abstract, the submission claimed N=69 (not supported by reference).

[b] Only patients receiving eculizumab peri-transplant were included in the data presented.

[c] Duration of follow-up post transplant.

[d] At last reported follow-up.

Source: Table constructed during the evaluation.

6.35 A total of 98 previously un-assessed cases of prophylactic peri-transplant use of eculizumab in renal transplant patients were presented in the submission. Of the 98 patients 95 (97%) maintained satisfactory allograft function over the duration of follow-up ranging from between 2 months to 5 years. Reoccurrence for TMA was reported in 6 patients (6%). Two of the individual case reports included patients who had discontinued eculizumab post transplant with no recurrence of TMA at follow up of 1 year and 6 months (after a liver transplant) after discontinuation.

ii) Post-transplant and sustained use of eculizumab in patients after renal transplantation

6.36 The outcomes for use of post-transplant eculizumab in patients after renal transplantation are summarised in Table 6.

Table 6: Summary of new data presented in the submission with post-transplant eculizumab treatment.

	Siedlecki 2016	Andrade 2016
	Post-transplant N=36[a]	**Post-transplant N=3**
Median age at transplant, years	34.4	28.1 ± 22
Family history of aHUS N (%)	3 (8%)	NR
CFH mutation detected N (%)	NR	NR
Dialysis post transplant N (%)	*12 (33%)*	NR
Duration of time to dialysis, median (range), months	*1.6 (0.1 - 15.0)*	NA
Duration of follow-up[b],	Up to 12 months	Eculizumab treatment 11.5 months ± 7.2
Serum creatinine, mean (SD), µmol/L[c]	*NR*	0.9±0.3 mg/dL
Recurrence of TMA in patients N	22 (61%)	NR
Duration of time to TMA, median (range), months	3.0 (0.2 – 8.7)	NA
Satisfactory allograft function at last follow-up, N (%)	NR (24 inferred by no dialysis required)	1 2 deaths with functional grafts
Death (all causes) N (%)	0	2 (pulmonary infection)

A = not applicable; NR = not reported; SD = standard deviation; TMA = thrombotic microangiopathy; Ec = eculizumab
[a]Numbers reported as per the provided abstract, the submission claimed N=78 (not supported by reference).
[b] Duration of follow-up post transplant.
[c] At last reported follow-up.
Source: Table constructed during the evaluation.

6.37 At total of 17 of 39 (42%) patients remained free of recurrent TMA at the end of the follow up period of approximately 1 year with approximately 24 (61%) who maintained satisfactory allograft function at follow-up. However, 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 TMA. 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.

iii) Treatment of aHUS with long-term dialysis.

6.38 The outcomes for the use of long-term dialysis in aHUS patients are summarised in Table 7. A total of 26 new individuals with diagnosed aHUS were included in the studies with a further 2,458 patients with HUS (not confined to aHUS) reported more broadly without individual patient data being available.

Table 7: Summary long term dialysis treatment in ESRD due to aHUS.

	Durkan 2016 N=14 (9 relevant)	Neuhaus 1997 N=7	Besbas 2017 N=8[a]	Brunelli 2015 N=217		Sexton 2015 N=2,241	Case reports N=2
				Case N=217	Control N=1085		
Median age at diagnosis, years	13.2 (3.3–176.6	4.9 (3 days – 13.8 years)	NR	48±18	48±16	NR	6 and 17 months
Family history of aHUS N (%) CFH mutation detected N (%)	4 (29%) 3/7	NR NR	NR NR	HUS not specific to aHUS With ESRD	Matched cohort with ESRD	HUS not specific to aHUS With ESRD	NR 1
Dialysis required 1 year follow-up	9/11		NR	NR	NR	NR	2
Duration of follow-up[c], median (range), years	16.1 (1.7 – 19.1)	5.5 (0.5 – 23.4)	1.7	1.5[d]	1.7[d]	3.7 (listed for transplant) 3.8 (post transplant) 5.4 (to death)	1 15 (no transplant)
Serum creatinine, mean (SD), µmol/L[e]	219[f] (99–1253)	566 (Median at admission)	NR	NR	NR	NR	147[f] NR
Recurrence of TMA in patients N	9	6/19 (36%)[g]	NR	176 (81%) All hospitalisations	719 (66%) All hospitalisations	NR	0 (transplant)
Duration of time to TMA, median (range), months	11.4 (4.3 – 21.5)	NR	NR	NR	NR	NR	NR
Dialysis continuing at last follow-up N (%)	1	2	1	217 (100%)	1085 (100%)	NR	1
Satisfactory allograft function at last follow-up, N (%)	5 (36%) 2 NRF	NR	7 (1 renal transplant)	NA	NA	24.2% (received transplant)	1/1
Death (all causes) N (%)	5 (36%)	2 (29%)	0	39 (18%) 12.4[h]	204 (19%) 11.0[h]	44.8%	0

NA = not applicable; NR = not reported; SD = standard deviation; TMA = thrombotic microangiopathy; Ec = eculizumab; NRF = normal native renal function

[a] The study did not provide enough information to derive ESRD patients individually.

[b] Only patients receiving eculizumab peri-transplant were included in the data presented.

[c] Duration of follow-up post transplant.

[d] Mean follow-up time on dialysis

[e] At last reported follow-up.

[f] Highest level recorded.

[g] All surviving patients not ESRD.

[h] Mortality rate per 100 patient years at risk.

Source: Table constructed during the evaluation.

6.39 From the use of long term dialysis in ESRD in HUS dialysis was stopped in several patients that had received renal transplants with successfully functioning allografts at last follow-up. Overall deaths from all causes ranged from 18% to 44.8%. However, the number of deaths specifically related to complications due to aHUS could not be quantified.

iv) Prophylactic plasma exchange/plasma infusion in aHUS patients undergoing renal transplant

6.40 The outcomes for the use of prophylactic plasma exchange/plasma infusion in aHUS patients undergoing renal transplant are summarised in Table 8. A total of 28 new cases which had not previously been presented to the PBAC were submitted.

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Table 8: Summary Prophylactic plasma exchange/plasma infusion in aHUS.

	Le Quintrec 2013 N = 9	Ardissino 2016 N = 5[a]	Jananko 2008 N = 2	Davin 2008 N=2	Case reports N-= 10
Median age at diagnosis, years	32	NR	1 and 16	3 and 4	8.1 (6 months-31)
Family history of aHUS N (%) CFH mutation detected N (%)	9/57 (16%) 18/57 (32%)	NR	Related patients 2 (100%)	Sisters 2	4 (40%) 6 (60%)
Duration of PE/PI peri-transplant	NR	NR	6 months (both)	1 day	1 day (1 no per/1 3 years)
Duration of PE/PI post transplant	NR	NR	NR	2 × daily for 7 days 1 × weekly 2months then bi weekly 1 × weekly	17 days -36 months
Dialysis required post transplant, N	NR	NR	0	0	2 (20%)
Recurrence of TMA in patients N	3 (33%)	1.4 (event/patient/10 yrs)	0	2	4 (40%)
Satisfactory allograft function at last follow-up, N (%)	9 (3 rescued with Ec post TMA)	4	2 (15 and 9 months follow-up)	1	8 (2 rescued with EC post TMA) (1 was not able to be stabilised with Ec after TMA)
Death (all causes) N (%)	0	0	0	0	0
Other related information	pre-emptive plasmatherapy decreased graft loss RR = 0.11 [0.01–0.84] p = 0.035 decreased disease recurrence RR = 0.34 [0.10–1.13] p =0.078.	All patients received Ec when it became available.	Both patients received liver-kidney transplants	A second monozygotic twin did not require a transplant after native kidney was rescued by weekly and then biweekly PE indefinitely with 6 years follow up. Twin one had PE intensified to daily during two TMA recurrences with functionality restored	Length of post transplant PE/PI very variable. One case report was a follow up 3rd transplant on 1 patient in Davin 2008. Follow up varied from not reported up to 5 years

NA = not applicable; NR = not reported; TMA = thrombotic microangiopathy; Ec = eculizumab

[a] Abstract only available.

Source: Table constructed during the evaluation.

6.41 The outcomes for the use of PE/PI in aHUS patients receiving a renal transplant above, did not include any deaths during the reporting period of the individual studies. There was significant use of eculizumab post PE/PI (separate to those reported in Table 9 below) which had a confounding effect on the applicability of the outcomes of survival and allograft function.

v) Post TMA initiation of eculizumab in aHUS patients who have undergone a renal transplant

6.42 The outcomes for the use of post TMA event eculizumab in aHUS patients after renal transplant are summarised in Table 9. Patients included in previously submitted studies from the March 2016 submission were excluded from the below table.

Table 9: Summary eculizumab treatment post TMA in renal transplant patients.

	Sheerin 2015 N=1	**Zuber 2012 N=11[a]**	**Case reports N-= 6**
Mean age at diagnosis, years	NR	15.4 (1day – 34years)	23 (1 – 48 years)
Family history of aHUS N (%)	NR	NR	2 (33%)
CFH mutation detected N (%)	NR	5 (45%)	2 (33%)
Time to TMA post transplant	NR	3 days – 5 years	6 day – 4 years
Other treatments post transplant	NR	10 PE	4 PE
Time from TMA to Ec	NR	1 day – 8 months	4 days - 5 weeks
Dialysis required post transplant, N	0	2	0
Mean duration of Ec treatment	Ongoing	13.9 months (1day – 43 months)	20.5 months (7 months – 3 years)
Satisfactory allograft function at last follow-up, N (%)	1	10	6
Death (all causes) N (%)	0	0	0
Other related information	Single patient form a retrospective cohort study	Majority had PE post TMA which either not tolerated or relapsed. 1 patient had graft function recovered after HD with Ec.	Significant heterogeneity in time to TMA post transplant and treatment post TMA.

NA = not applicable; NR = not reported; ; TMA = thrombotic microangiopathy; Ec = eculizumab; PE = plasma exchange; HD = haemodialysis

[a] Includes literature search patient not previously reported.

Source: Table constructed during the evaluation.

6.43 From the further 18 patients where eculizumab was initiated post TMA no deaths were recorded with 2 patients requiring post transplant dialysis (1 long term) and 17 (94%) with satisfactory allograft function at the last reported follow-up.

6.44 The PBAC considered that while the data was not robust it did demonstrate that eculizumab reduces the risk of recurrence of aHUS following kidney transplantation (and graft loss). However, the PBAC was unable to quantify the incremental benefits of eculizumab treatment over (a) best supportive care (b) changes in the duration of treatment; or (c) of prophylactic treatment vs treatment upon recurrence.

Comparative harms

6.45 The PBAC previously 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 TMA and renal function is also not known (Eculizumab PSD, March 2014 PBAC Meeting). No data were submitted to address this issue. The PBAC noted that in its pre-PBAC response the sponsor claimed that there was up to 10 years of treatment data available for eculizumab internationally, however these data were not presented to the PBAC for consideration.

Clinical claim

6.46 The submission claimed that eculizumab is effective in preventing post-transplantation recurrence of TMA and graft loss.

6.47 The PBAC considered that the claim of effectiveness in preventing post-transplantation recurrence of TMA and graft loss due to recurrent aHUS was reasonable. However, given the lack of comparative data, and the heterogeneity in the evidence base, the PBAC concluded that it was not possible to precisely quantify the comparative benefits and harms of prophylactic eculizumab, initiated peri-transplantation, compared to either supportive care or the alternative treatment approach of initiating treatment at post-transplantation recurrence of TMA. There was also 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.

Economic analysis

6.48 The submission did not present an economic analysis.

Drug cost/patient/year:

6.49 For an adult patient weighing at least 40kg (assumes inpatient and ongoing maintenance treatment):

- Initial phase: 900mg weekly x 4, $71,250/patient (public), $71,813/patient (private)
- Initial phase with additional dose at graft reperfusion: $89,063/patient (public), $89,766/patient (private)
- Maintenance phase: $617,500/patient/year (public), $622,381/patient/year (private) (assuming 1200 mg every 2 weeks = 4 vials ×(52 weeks ÷2) = 104 vials per year).

6.50 Based on the recommendation proposed by the PBAC the cost per course was $118,750/patient (public), $119,690.40/patient (private).
- assuming 1200 mg every 2 weeks = 4 vials ×(10 weeks ÷2) = 20 vials per treatment course.

Estimated PBS usage & financial implications

6.51 The submission used an updated epidemiological approach to estimate the prevalent number of patients with aHUS who have ESRD, who are likely to be treated prophylactically with eculizumab when undergoing renal transplantation.

6.52 The submission applied a transplantation rate of 22.7% (an average transplantation rate across all age groups from 0-84 years as listed in the ANZDATA report) to a prevalent pool of ESRD patients with a diagnosis of aHUS of [redacted] to estimate that [redacted] patients would initiate treatment under the proposed restriction in the first year of listing.

6.53 The PBAC did not consider that the use of overall transplantation rates was applicable in this setting as aHUS patients with ESRD, because these data included many who would not be wait listed or be considered for a living related transplant. The PBAC considered that the rate of transplantation in the aHUS was likely to be considerably higher given their younger age and absence of comorbidities. The PBAC considered that the prevalent pool was more representative of the probable uptake within the first few years of listing.

6.54 The submission claimed that with the availability of eculizumab for patients with active and progressing TMA, the number of patients progressing to ESRD over time will decrease and hence the number of patients initiating treatment decreased in the financial estimates to 2 by year 5. The PBAC considered that a reduction in aHUS patients reaching ESRD was reasonable however the level of reduction was uncertain.

6.55 The submission provided financial estimates based on the predicted number of initiating and maintenance patients based off the March 2014 submission estimated average number of vials. It was noted that the estimated number of vials used per patient in the maintenance phase of [redacted]/year is lower than the current maintenance dose in the Prescribing Information of 1200 mg every 2 weeks or 104 vials/person/year. It is not clear if this was done to account for some patients only receiving treatment for part of a year. The evaluation recalculated the cost to the PBS if the PI recommended dose was used in all patients.

Table 10: 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 of aHUS patients with ESRD eligible for renal transplantation after taking into account deaths and incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of deaths whilst awaiting renal transplant [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident patient with ESRD [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients undergoing renal transplantation per year [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients likely to be treated i.e. patients who have a medium to high risk of subsequent TMA post renal transplantation [d]					
Patients on maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiating patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients treated with eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vials per year [e]					
Patients on maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiating patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total vials per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS [f]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Vials per year based on prescribing instructions [g]					
Patients on maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiating patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total vials per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS [g]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Number of deaths whilst awaiting renal transplant is based on an annual death rate per 100 patient-years during renal replacement therapy of patients under the age of 85 (Source= ANZDATA 38th report, chapter 3, Table 3.3). Deaths are assumed to occur at end of each year.

[b] Assuming [redacted] new patients with aHUS will progress to ESRD every year. This assumption is likely to overestimate the number of incident cases and cost to the PBS.

[c] Assuming a transplantation rate of 22.7% per year in patients under the age of 85. This rate includes both deceased and living donor allograft (source= ANZDATA 38th report, chapter 8, Figure 8.4.1).

[d] High-medium risk of subsequent TMA is defined as any of the following: Mutations in Factor H or gene re-arrangements involving Factor H and Factor H related proteins OR Gain of function mutations in Factor B or C3 OR Previous early recurrence OR Loss of previous transplant due to recurrent aHUS OR No identified mutation or autoantibody OR Mutations in Factor I OR Variant of uncertain significance OR Detectable autoantibodies against CFH. Low risk of subsequent TMA is defined as any of the following: Isolated Mutation in Membrance cofactor protein (CD46) OR persistently negative FH autoantibodies (Source= UK Renal Association Guidelines [2013], KDIGO [2016], and Zuber [2012]).

[e] Assuming [redacted] vials in new patients and [redacted] vials in patients on maintenance based on the November 2013 PBAC submission assumption considered by the PBAC at its March 2014 meeting. 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 discretional use of an additional 900 mg dose following graft reperfusion.

[f] Based on the public dispensed price per maximum quantity of $5,937.50. Patient co-payment, private hospital mark up and dispensing fee have not been taken into consideration. Due to the small number of patients, no attempt has been made to present these estimates by patient category.

[g] Assuming [redacted] vials in new patients and [redacted] vials in patients on maintenance based 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 discretional use of an additional 900 mg dose following graft reperfusion.

6.56 The redacted table shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be $10 - $20 million per year.

6.57 The PBAC did not consider that the financial estimates as presented by the sponsor, and adjusted during the evaluation, were informative as they included low patient uptake in all of the projected years and were largely driven by continued maintenance treatment which was not supported. The PBAC considered that the financial implications of listing would need to be recalculated on the basis of the PBAC's recommendation.

Risk Share Arrangements

6.58 The PBAC noted the risk sharing arrangement proposed in the pre-PBAC response. The PBAC considered that a risk share with a hard cap based on the revised estimates would be appropriate.

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

7 PBAC Outcome

7.1 The PBAC recommended extending the listing of eculizumab, on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program): Authority Required (WRITTEN) listing for the prevention of atypical haemolytic uraemic syndrome (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. The PBAC recommended prescribing should be restricted to prescribing by a nephrologist or a paediatric nephrologist within a transplant unit.

7.2 The PBAC considered that a separate restriction for this indication was appropriate.

7.3 The PBAC considered that in-patient treatment should not be subsidised by the PBS. The PBAC further considered that initial treatment in this setting should be limited to 3 months of treatment post transplant (comprising the period of in-patient treatment plus 10 weeks of treatment under the PBS) as this is the highest risk period for TMA due to aHUS recurrence.

7.4 The PBAC noted that patients with recurrence of TMA due to aHUS after this time would be eligible for eculizumab under the current listing.

7.5 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.

7.6 The PBAC did not consider the financial estimates or the Risk Sharing Arrangement proposed by the sponsor to be informative as they included continuing treatment beyond the recommended 10 weeks. The PBAC noted the financial estimates would need to be recalculated on the basis of the PBAC's recommendation and considered that a risk share with a hard cap based on the revised estimates would be appropriate.

7.7 The PBAC again recommended 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.

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

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ECULIZUMAB 300 mg/30 mL injection, 30 mL vial	1	0	Soliris®	Alexion Pharmaceutical Australia Pty Ltd.

Category/ Program	Section 100 – Highly Specialised Drugs Program
Condition:	Atypical haemolytic uraemic syndrome (aHUS)
PBS Indication:	Atypical haemolytic uraemic syndrome (aHUS)
Restriction level:	☒Authority Required - In Writing
Treatment criteria:	Must be treated by a paediatric nephrologist OR Must be treated by a nephrologist AND Must be treated in a transplant unit.
Clinical criteria:	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 10 weeks.
Prescriber Instructions:	High risk of recurrent aHUS in the allograft is defined as follows: (i) Mutations in Factor H or gene re-arrangements involving Factor H and Factor H related proteins; OR (ii) Gain of function mutations in Factor B or C3; OR (iii) Loss of previous transplant due to recurrent aHUS Medium risk of recurrent aHUS in the allograft is defined as follows: (i) No identified mutation or autoantibody; OR (ii) Mutations in Factor I; OR (iii) Mutation of uncertain functional significance; OR (iv) Detectable autoantibodies against FH The authority application must be in writing and must include: (1) Two completed authority prescription forms; and (2) A completed aHUS eculizumab Authority Application Supporting Information Form aHUS renal transplant; and (3) The date of the renal transplant; and (4) A detailed cover letter from the prescriber; and (5) A copy of a current Certificate of vaccination or a statement that vaccination has or will be administered and appropriate antibiotic prophylaxis has been prescribed; and (6) Evidence of medium to high risk of TMA; and (7) Evidence that the cause of end stage renal disease was due to aHUS. A patient may qualify for PBS-subsidised treatment under this restriction once only per allograft.
Administrative Advice	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Written applications for authority to prescribe must be submitted to Department of Human Services. Human Services will then contact the prescriber by telephone. The Authority application must be accompanied by a cover letter from the prescriber, providing complete details on: a) Clinical and laboratory/biopsy details describing the cause of end stage renal disease; b) Results of testing for genetic mutations; c) Family history of aHUS, especially in first-degree relatives; d) History of renal or other organ transplant; e) Any other matters considered relevant by the prescriber.

	The Authority application should include the results of screening for genetic mutations known to confer a high risk of developing aHUS. The results of genetic screening should be provided whether or not a high-risk mutation has been identified. WARNING: Eculizumab increases the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection. At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug for up to 10 weeks, according to the specified dosage in the approved Product Information (PI). 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. Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.

9 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.

10 Sponsor's Comment

Alexion is pleased that the PBAC has recommended extending the listing of Soliris (eculizumab) to facilitate renal transplantation in patients with ESRD due to aHUS. All published and available evidence demonstrates that the risk of TMA manifestations is highest within the first year of transplantation. Alexion is therefore concerned that the PBAC recommendation to administer therapy for only 3 months is not evidence-based and could place high risk patients (who have already experienced ESRD and required a renal transplant) at risk of subsequent TMA and graft failure. Alexion proposed a risk sharing agreement in the pre-PBAC response, and is willing to work collaboratively with the Department and PBAC to find a solution to ensure evidenced-based, safe and equitable care for transplant patients with aHUS. This includes an appropriate duration of therapy with eculizumab and coverage of inpatient treatment.