Eculizumab, concentrated solution for I.V. infusion, 300 mg in 30 mL, Soliris® - March 2013

PUBLIC SUMMARY DOCUMENT
Product: Eculizumab, concentrated solution for I.V. infusion, 300 mg in 30 mL, Soliris®
Sponsor: Alexion Pharmaceuticals Australasia Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested a Section 100 (Highly Specialised Drugs Program) listing or inclusion on the Life Saving Drugs Program (LSDP) for treatment of atypical Haemolytic Uraemic Syndrome (aHUS).

Highly Specialised Drugs Program:
Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

Life Saving Drugs Program:
Through the Life Saving Drugs Program (LSDP), the Australian Government provides subsidised access, for eligible patients, to expensive and potentially life saving drugs for very rare life-threatening conditions.

Before a drug is made available on the LSDP, it must generally be accepted by the Pharmaceutical Benefits Advisory Committee as clinically necessary and effective, but not recommended for inclusion on the Pharmaceutical Benefits Scheme due to unacceptable cost-effectiveness.

2. Background

Eculizumab had not been previously considered by the PBAC for treatment of patients with aHUS.

Eculizumab is currently available through the Life Saving Drugs Program (LSDP) for treatment of eligible patients with paroxysmal nocturnal haemoglobinuria (PNH).

3. Registration Status

Eculizumab is currently TGA registered for the following indications:

- For the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) to reduce haemolysis.
- Atypical haemolytic uraemic syndrome (aHUS).

4. Listing Requested and PBAC's View

Listing was requested under the Section 100 Highly Specialised Drugs Program, or the Life Saving Drugs Program for treatment of atypical Haemoytic Uraemic Syndrome. No restriction wording was proposed in the submission.

5. Clinical Place for the Proposed Therapy

Eculizumab was proposed to be used in patients diagnosed with aHUS and with symptoms of thrombotic micro-angiopathy (TMA), a condition caused by several different underlying conditions. When the underlying cause is aHUS, TMA causes end-organ ischaemia and infarction and most commonly affects renal function. The diagnosis of aHUS is confirmed by exclusion of other conditions causing TMA which includes Shiga-toxin E.coli (STEC) infection, thrombotic thrombocytopaenic purpura (TTP), malignancy, HIV or common drugs associated with inducing TMA.

The PBAC noted an incidence of aHUS which is approximately 1-2/100,000 in the general population and 6/100,000 in children. The PBAC also noted that the submission did not adequately address the place of eculizumab in the management of aHUS with respect to the treatment of newly diagnosed patients versus patients who have previously been adequately treated with plasma therapy.

The PBAC considered the clinical management algorithm for the treatment of aHUS, and the place of eculizumab in this algorithm, was unclear. The PBAC noted the following issues:

- the submission did not adequately describe the natural history of aHUS or the natural history of treatment with supportive care;
- draft 'Condition Guidelines' for the treatment of aHUS with eculizumab through the LSDP were not included with the submission;
- the submission did not adequately address the place of eculizumab in the management of aHUS with respect to the treatment of newly diagnosed patients versus patients who have previously been adequately treated with plasma therapy; and
- treatment with eculizumab can commence on an inpatient or outpatient basis. The Pre-Sub-Committee Response (PSCR, p1) states that diagnostic tests for aHUS will be conducted in the inpatient setting. It is not clear whether this means that treatment initiation is also expected to commence primarily on an inpatient basis.

Diagnostic testing

The proposed treatment algorithm for aHUS stated that at diagnosis, the ADAMTS-13 and Shiga-toxin producing *E coli* (STEC) tests will be used to exclude diagnosis of some other TMA-causing conditions. The submission identified that the majority of Australian laboratories have initial Shiga-toxin testing screening capabilities. Five laboratories were identified that could provide multiple polymerase chain reactions (PCR) testing for Shiga-toxin 1 (STEC1), Shiga-toxin 2 (STEC2), and PCR serotyping within 48 hours for urgent requests. The submission also identified four laboratories in Australia that currently offer ADAMTS-13 testing within 48 hours for urgent requests.

The PBAC looked at the usefulness of applying ADAMTS-13, STEC and genetic testing to define the population of patients with a diagnosis of aHUS. The STEC test is performed to exclude those patients who have STEC-HUS which causes diarrhoea and is associated with typical HUS. The ADAMTS-13 test is performed to exclude patients who have thrombotic micro-angiopathy (TMA) due to thrombocytopenic purpura (TTP). For the STEC and ADAMTS-13 tests, the PBAC stated it was not clear how these tests fit in the treatment algorithm with regard to timing of test results and initiation of treatment.

The PBAC noted that the results of ADAMTS-13 and STEC testing are not available immediately, taking at least 24 to 48 hours. This could result in patients with TTP or typical HUS being treated with eculizumab before definitive diagnosis. Additionally, rapid access to

treatment would not allow identification of the natural resolution of the acute phase in some patients, which could result in unnecessary over-treatment.

The PBAC noted that the accuracy of diagnosis is uncertain as there is uncertainty about sensitivity and specificity for both tests (STEC and ADAMTS-13), and this was not considered in the submission..

The PBAC also noted that the thresholds for exclusion of TTP using ADAMTS-13 testing varied between the eculizumab clinical trials (>5%) and the literature (>10-20%). The PBAC also noted that the ADAMTS-13 testing has limited availability and results may not be available immediately. As such, the PBAC was unsure that eculizumab would be able to be used at the point of diagnosis. The PBAC noted that the submission's treatment flowchart implied early diagnosis and treatment commencement, but this may not be realistic.

The PBAC noted that different genetic mutations may be associated with different renal and mortality outcomes (Noris 2010). Genetic testing was not used as part of the entry criteria in the eculizumab studies and has not been included in the management algorithm presented in the submission.

The PBAC acknowledged that genetic mutation testing for aHUS is not yet available in Australia and would not have a role in confirming the initial diagnosis of aHUS due to the need to make a rapid treatment decisions for a patient presenting with HUS symptoms. However, the PBAC considered that it might be appropriate for the eligibility for ongoing treatment with eculizumab to be targeted according to the presence or absence of certain membrane cofactor protein (MCP) mutations, noting that there is some evidence (Caprioli, Noris et al. 2006; Noris and Remuzzi 2009; Zuber, Quintrec et al. 2012) that mutations of MCP have a relatively good prognosis with a complete remission rate of 80-90% and little chance of graft rejection after kidney transplant. Conversely patients with mutations in the CFH, CFI, CFB and C3 genes have a much poorer prognosis and for patients with CFH and CFI mutations, a very high chance of recurrence of disease following kidney transplant.

The PBAC noted that it remained unclear as to whether some STEC or ADAMTS-13 testing might take place where an MBS item code is required. Complete STEC testing according to the submission costs around $340/test. The submission reported that this test is covered under MBS item number 69494. This item covers: Detection of a virus or microbial antigen or microbial nucleic acid (not elsewhere specified) and has a scheduled fee of $28.85. No MBS item exists specifically for diagnosis of STEC.

For ADAMTS-13, the submission noted that an urgent test costs $300-$450 (mean = $323/test). The PBAC noted that there is currently no MBS item for this testing. However, if it is always performed in a public hospital as an inpatient service, an MBS item would not be required. The submission did not discuss whether this test would normally be performed on an inpatient or outpatient basis. If the test is performed on an outpatient basis or in a private hospital, an integrated co-dependent submission would be required to support a listing.

6. Comparator

The submission nominated supportive care, consisting of plasma exchange/plasma infusion (PE/PI), dialysis and/or renal transplant, as the comparator.

The PBAC considered that supportive care consisting of PE/PI was an appropriate comparator if eculizumab is initiated early in the treatment of the condition. However, the PBAC considered that renal dialysis, renal transplant, and renal-hepatic transplant were the appropriate comparators in studies looking at treatment of later stages of the condition.

The PBAC noted that treatments in addition to PE/PI such as corticosteroids, anti-anaemic preparations such as darbepoetin alpha, anti-thrombotic agents, heparin, beta-blockers and calcium channel blockers were not included when describing supportive care. In addition, the PBAC noted that some use of rituximab has also been reported in the case studies presented in the submission.

The PBAC stated that it was not clear exactly which supportive care therapies would be replaced by eculizumab treatment.

7. Clinical Trials

The submission presented two prospective open label single arm studies (combined n=37) of eculizumab for aHUS (studies C08-002 and C08-003). In addition, one retrospective observational study (C09-001r) (n=30) of eculizumab for aHUS, and five observational studies of supportive care for aHUS (n=710) were included in the submission.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Best supportive care		
Noris 2010	Relative Role of Genetic Complement Abnormalities in Sporadic and Familial aHUS and Their Impact on Clinical Phenotype.	Clinical Journal of The American Society of Nephrology 2010; 5. 1844-59**.**
Kremer Hovinga 2010	Survival and relapse in patients with thrombotic thrombocytopaenic purpura.	Blood 2010*;* 115(8): 1500-1511.
Taylor 2004	Clinico-pathological findings in diarrhoea-negative haemolytic uraemic syndrome.	*Pediatric Nephrology* 2004;19:419-425.
Caprioli 2006	Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome.	*Blood Cells Molecules & Diseases* 2006; 108(4): 1267-1279.
Sellier-Leclerc 2007	Sellier-Leclerc, A., *et al*. Differential Impact of Complement Mutations on Clinical Characteristics in Atypical Hemolytic Uremic Syndrome.	Journal of the American Society of Nephrology 2010; (18): 2392-2400.

8. Results of Trials

The PBAC noted that the two prospective eculizumab studies (C08-002 and C08-003) were single arm and all other studies included were retrospective studies, therefore the risk of bias in the studies was considered to be high.

The outcomes reported in C08-002 and C08-003 studies were haematologic normalisation, platelet count change, risk of TMA event, renal function and quality of life. The results

showed that compared to baseline, eculizumab reduced the TMA intervention rate. Improvements were also observed with eculizumab treatment for outcomes related to eGFR function, quality of life and platelet count (C08-002 only).

For the supportive care studies, the PBAC considered that the differences in follow up periods, inclusion criteria, type of HUS and type of patients (paediatric or adult) did not enable any comparison to be made between mortality rates in the supportive care studies. Differences in selection, the number of patients lost to follow up and the treatment received in each study may also have an impact on the comparability of individual studies. Additional relevant data on mortality and renal failure were extracted during the evaluation for the two studies (Kremer-Hovinga 2010 and Noris 2010) considered most similar to the eculizumab trials.

Limited data on renal function were presented for the supportive care studies. Selected data were extracted during the evaluation. In Kremer Hovinga 2010, 109 (54%) of patients experienced acute renal failure in their first episode of aHUS and subsequently 54 (50%) of these patients recovered normal creatinine levels.

Noris 2010 presented outcomes at 1 year (of n=149 children and n=99 adults) and 3 years (of n=146 children and n=94 adults) after onset of aHUS. At one year 22.9% of children and 47.2% of adults had end-stage renal failure rising to 33.3% and 62.4% at three years, respectively.

As renal function was reported differently in the eculizumab and supportive care studies, the PBAC considered that it was difficult to draw any comparisons.

The PBAC noted that despite the basis of the submission's economic claim being life years saved, comparative mortality data were not presented. The PBAC noted the yearly probability of death for eculizumab and supportive care, calculated during the evaluation, suggested no difference in mortality rate for eculizumab and supportive care patients. The sponsor argued that the mortality rate for supportive care from Kremer Hovinga 2010 had been incorrectly calculated by the evaluators. The ESC acknowledged the information provided by the sponsor but considered that the mortality data remained uncertain. Similarly, the PBAC acknowledged that the mortality estimates were uncertain.

Overall, the PBAC deemed that there was inadequate information presented to confirm that the "supportive care" studies are sufficiently comparable to the eculizumab single-arm studies for a valid assessment of the effect on survival.

The PBAC noted that there was not sufficient evidence presented to support the sponsor's claims that "the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease." The magnitude of the reduction in life expectancy associated with aHUS was not adequately described in the submission.

The submission did not provide any additional data on potential safety concerns for eculizumab beyond those identified in the clinical trials. The reported drug related adverse events included headache, leukopenia and lymphopaenia. However, comparative assessment of the safety of eculizumab and supportive care were not presented.

The PBAC noted with concern that patients treated with eculizumab are more susceptible to meningococcal infection. It was also noted that the submission contained a recommendation that all patients should receive *Neisseria meningitidis* vaccination at least two weeks prior to eculizumab treatment. In all patients aged less than two years of age, and in patients where two weeks has not elapsed between vaccination and initiation of treatment, antibiotic prophylaxis is recommended.

The PBAC's view was that in light of the cases of meningococcal infection reported in the clinical studies of eculizumab in the treatment of PNH, insufficient protection is afforded to patients through *Neisseria meningitidis* vaccination alone during eculizumab therapy. This limits the sole use of this treatment and affects the economic analysis and financial implications.

9. Clinical Claim

The submission described eculizumab as safer and more effective than supportive care "in treating newly diagnosed and long-term aHUS, and in patients with renal transplant to avoid renal and extra-renal TMA and graft loss". The PBAC considered that this claim was not adequately supported for the following reasons:

- Direct comparative data were not available
- The studies included had a high risk of bias, which is likely to favour eculizumab
- Different outcomes were measured in the eculizumab studies compared to the supportive care studies
- The submission did not provide an adequate comparison of comparative mortality
- The submission did not provide comparative evidence of safety concerns with current supportive care, as such there were no data included in the submission to assess the basis of superior safety.
- It is unclear whether the supportive care studies were the most appropriate studies available in the literature, as insufficient details on the literature search were provided.

10. Economic Analysis

The submission presented an economic evaluation (cost effectiveness and cost utility analyses), based on claims of superior efficacy. The ICERs were estimated to be greater than $2 million per life year gained (LYG) and between $1 - $4 million per quality adjusted life year (QALY), based on taking mortality and utility outcomes from the prospective trials, and an estimated mortality outcome from the supportive care studies applied to the Australian aHUS population.

The PBAC considered that the economic claim was unjustified because it was based on mortality rates that were considered uncertain by the PBAC.
The PBAC considered that the ICER was likely to be substantially higher than that estimated in the submission because:
- costs of the eculizumab arm were underestimated and no infusion, vaccination, monitoring, dialysis, plasma therapy or diagnostic costs were included;
- the cost of supportive care was overestimated with 37% renal transplants in one year, more dialysis than is likely to be required and double counting of the cost of transplant maintenance;
- the difference in mortality is overestimated and the model is highly sensitive to this rate;
- the utility values used for eculizumab and supportive care groups were inappropriate given that they were from a single arm study for eculizumab.

11. Estimated PBS Usage and Financial Implications

The submission estimated a total cost to the PBS of between $100 - $200 million over the first five years of listing. The submission assumed a treatment rate of approximately 50 percent of patients diagnosed with aHUS. There was no justification provided to explain this figure and in PBAC's view, the figure is likely to be higher than this leading to an increase in the net yearly cost to Government.

The PBAC agreed that the net cost per year was highly uncertain given the poor data on prevalence and incidence of aHUS in Australia and uncertainty as to whether the European paediatric prevalence data are applicable to the overall Australian population.

The PBAC agreed that the estimates are highly sensitive to any small change in patient numbers due to the high acquisition cost of eculizumab.

The PBAC noted that the eculizumab Product Information allows for the use of more frequent dosing (12 days) than the recommended 14 days. Use of 12-day dosing rather than 14-day dosing would substantially increase the financial estimates. This was not accounted for in the submission.

The PBAC noted that no information was provided on the increased costs to the MBS, NIP or PBS for infusion, meningococcal vaccinations, prophylactic antibiotics and ADAMTS-13 and STEC diagnostic testing costs.

The PBAC noted that there is a high potential for eculizumab use outside the aHUS population given the potential for treatment that is not consistent with the treatment algorithm provided.

In the event that the diagnostic processes used to identify aHUS patients do not discriminate aHUS from other conditions with adequate accuracy, the PBAC was concerned that additional patients may be treated with different benefit or patients treated who would not benefit.

12. Recommendation and Reasons

The PBAC acknowledged the difficulties associated with obtaining clinical data for the use of eculizumab in the treatment of patients with aHUS disease given the rarity of the condition.

The PBAC noted that identification of the appropriate comparator remained difficult when the place of eculizumab in the clinical management of aHUS was unclear.

The PBAC noted that limited details were included in the submission on the testing required for definitive diagnosis of aHUS, and it was the PBAC's view there are likely to be implications for the Medical Benefits Scheme (MBS).

The PBAC considered that the place of eculizumab in the clinical management of patients with aHUS remains unclear and noted inconsistencies between the submission algorithm and the submission's description of the appropriate PBS population, which made the assessment of the applicability of the trial results to the PBS population, and estimates of use, difficult.

The PBAC considered that the clinical evidence provided in the submission was not sufficient to support the claim that eculizumab is safer and more effective than supportive care in treating newly diagnosed and long-term aHUS, and in patients with renal transplant to avoid renal and extra-renal TMA and graft loss. Most clinical outcomes from the studies presented in the submission were unable to be directly compared, and therefore the risk of bias in estimates of effect from the studies was high. Better data on the treatment of acute manifestations of the disease and long term treatment would be required.

The PBAC therefore rejected eculizumab for PBS listing under Section 100 due to uncertainty regarding clinical effectiveness and unacceptable cost-effectiveness in treating newly diagnosed and long-term aHUS, and in patients with renal transplant to avoid renal and extra-renal TMA and graft loss.

The PBAC considered that eculizumab did not meet the criteria for approval through the 'Rule of Rescue' because the submission did not adequately describe the natural history of aHUS or the natural history of treatment with supportive care. In addition, the PBAC was not provided with adequate evidence to demonstrate that the drug provides a clinical improvement sufficient to qualify as a rescue from the medical condition. Further, the PBAC noted that PE/ PI, dialysis and/or renal transplant represent alternative non-pharmacological treatments for this condition.

The PBAC rejected eculizumab for inclusion on the LSDP because the PBAC considered eculizumab failed to meet criteria 1, 2, 3, 4, 5 and 7 due to reasons described below.

In relation to LSDP criterion 1, the PBAC agreed that aHUS is rare and clinically definable disease, but did not agree at this time that eculizumab is a proven therapeutic modality in newly diagnosed and long-term aHUS, and in patients with renal transplant to avoid renal and extra-renal TMA and graft loss, based on this submission.

Based on the information provided in the submission, the PBAC was not confident that the disease would be identifiable with reasonable diagnostic precision using the proposed treatment algorithm and associated testing procedures therefore LSDP criterion 2 was not met. It was not clear if diagnosis by exclusion of thrombocytopenic purpura (TTP) and Shiga-toxin producing *E.coli* infection HUS is adequate to definitively diagnose aHUS, and the diagnostic accuracy of the tests was not adequately described.

The PBAC did not agree that the submission provided sufficient acceptable evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease. The absolute mortality rates in patients with aHUS remain uncertain, and the submission did not provide a reasonable evaluation of the mortality rates for supportive care. Therefore LSDP criterion 3 was not met.

The PBAC considered that LSDP criterion 4 was not met because the submission did not present adequate acceptable evidence to support the claim that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug.

While the PBAC agreed that the use of eculizumab in patients with aHUS failed to meet the required cost effectiveness criteria for PBS listing, the PBAC considered that the clinical effectiveness of the drug in treating newly diagnosed and long-term aHUS, and in patients

with renal transplant to avoid renal and extra-renal TMA and graft loss remained unproven.. Therefore LSDP criterion 5 was not met.

The PBAC stated that PE/PI, dialysis and/or renal transplant represent non-drug therapeutic modalities that are recognised by medical authorities as suitable and cost effective treatments for this condition. Therefore eculizumab failed to meet LSDP criterion 7.

The PBAC considered that any re-submission would need to include more robust data to support the clinical claim that eculizumab is safer and more effective than supportive care in treating newly diagnosed and long-term aHUS, and in patients with renal transplant to avoid renal and extra-renal TMA and graft loss. Refinements would need to be made to the proposed treatment algorithm and the evidence provided to support the reliability of associated testing procedures to improve the diagnostic precision with which the disease would be identified. Consideration should also be given to the submission of an application for PBS listing under Section 100 with the proposed price benchmarked against other monoclonal antibodies.

The PBAC noted that the submission is eligible for an Independent Review of the decision not to recommend listing on the PBS.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:
Rejected

13. 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.

14. Sponsor's Comment

The sponsor strongly disagrees with recommendations and rationale from PBAC that eculizumab for aHUS does not meet LSDP Funding Eligibility Criteria.

Eculizumab has been approved by the TGA for this indication. The sponsor believes these PBAC recommendations are in conflict with the body of worldwide clinical evidence for eculizumab as a treatment in aHUS.

The sponsor intends to work with the PBAC and resubmit to answer the committee's areas of uncertainty in their review and recommendations as soon as possible.