# Clinical advice meeting statement

**Pharmaceutical Benefits Scheme listing of eculizumab (Soliris®) for atypical haemolytic uraemic syndrome in the context of renal transplant**

A clinical advice meeting was held on 12 February 2016 to discuss the place of eculizumab (Soliris) 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.

Representatives of the Department of Health were also in attendance to facilitate the meeting and to support the Chair and members of the PBAC.

## Background - atypical haemolytic uraemic syndrome (aHUS)

aHUS is a chronic, rare, progressive condition that causes severe inflammation of blood vessels and the formation of blood clots in small blood vessels throughout the body, a process known as systemic thrombotic microangiopathy (TMA). TMA may cause end organ ischaemia and damage and in aHUS commonly affects renal function.

A genetic basis for the disease can only be established in about one-half of patients, and some, but not all, patients experience recurrent episodes. Some patients are diagnosed in infancy, while others may develop the disease only after encountering a trigger factor in adulthood.

Under the current PBS listing, aHUS patients with either their native kidneys or a renal allograft who have not progressed to end stage renal disease (ESRD) are eligible to receive eculizumab if they have evidence of active, progressive TMA and they meet the other restriction criteria.

The PBAC noted in March 2014 the significant morbidity and mortality for patients with aHUS who have progressed to ESRD and require long-term dialysis. However, based on the data presented by Alexion Pharmaceuticals Australasia (the sponsor of eculizumab), the Committee was unable to determine the efficacy and cost-effectiveness of eculizumab for prevention of recurrence of TMA following kidney transplantation.

It was noted at the 24 June 2014 eculizumab stakeholder meeting that data about use in these patients should become available over time and therefore, this additional indication could be reconsidered for subsidy in the future. The Department, on behalf of the PBAC, approached the sponsor in September 2015 to request a summary of data that have become available since the PBAC’s March 2014 consideration on the use of eculizumab for the treatment of aHUS in the context of kidney transplantation. This update is on the March 2016 PBAC agenda.

## Risk of onset of aHUS post transplantation

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*

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.

*Previous episode of aHUS leading to loss of graft*

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*

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. 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.

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*

There was no clear consensus among the clinicians regarding the use of ongoing eculizumab as a prophylactic measure. Some clinicians would prefer to continue eculizumab indefinitely until the triggers of aHUS are better understood through further research. Others have developed experience with managing patients who have discontinued the drug and opted to monitor closely for any re-emergence of the condition (by platelet count, haemoglobin, dipstick, etc).

It was considered that future clinical decisions about withdrawal of eculizumab may, in the future, be guided by high quality testing of complement function and increased understanding of the genetic basis for the disease. It was noted that complement function tests are not widely available at present, but genotyping was increasingly available.

It was noted that during the first three months following renal transplantation, patients are exposed to numerous potential triggers for complement activation and aHUS recurrence in the post-surgery phase, including ischaemia-reperfusion injury and the use of calcineurin inhibitors. Patient management then changes from three months post-transplant, with a reduction in potential triggers encountered.

The issue of alternative diagnosis for TMA in the post-transplant setting was discussed. It was noted that it can be challenging to distinguish aHUS from other differential diagnoses. For example antibody-mediated rejection may be present in a patient with thrombocytopenia and a kidney biopsy showing TMA. Complications of calcineurin inhibitor treatment may also present a challenge to establishing an accurate diagnosis. It was conjectured that some transplant teams may choose to commence eculizumab treatment under such circumstances.

Eculizumab would be administered as three further weekly doses of 900mg, with an increase to 1,200mg in the fifth week following transplant and ongoing dosing of 1,200mg every 14 days thereafter.

It was noted that the dosing strategy for prophylaxis is the same as for acute management of aHUS, based on the expectation that the potential TMA triggers encountered post-transplant represent a comparable level of risk to an acute episode. The approved Product Information (PI) provides no specific direction on dosing in peri- or post-transplant settings. Since the TGA registration of eculizumab for aHUS in October 2012, there have been no published updates on the drug’s pharmacokinetic or pharmacodynamic parameters. The absence of recent data to support dose, treatment frequency and treatment duration means that clinicians are forced to develop dosing strategies in the absence of robust evidence.

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

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.

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.

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

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.

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

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.

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.

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

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.

## Next steps

The PBAC will consider the updated clinical data provided by the sponsor at its March 2016 meeting, in the context of the insights offered at this clinical advice meeting.