

# **Eculizumab for aHUS: utilisation update**

## **Drug utilisation sub-committee (DUSC)**

***October 2020***

### **Abstract**

#### ***Purpose***

DUSC has previously undertaken analysis of eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) in September 2017 and February 2019. These analyses comprised a 24-month predicted versus actual utilisation analysis (2017) and an update to the previous utilisation report.

At its June 2020 meeting, DUSC requested an update to the previous reports and adding additional data on length of time on treatment (LoT) and date of death data (DoD). Consequentially, this latest analysis provides updated utilisation data, up to and including 31 May 2020; information on patient initiations up to and including 30 June 2020; and data on LoT, and DoD data.

#### ***Date of listing on the Pharmaceutical Benefits Scheme (PBS)***

1 December 2014

#### ***Data Source / methodology***

The analyses used data from the Services Australia (formerly known as the Department of Human Services) supplied prescriptions database and authority approval database for dates of supply up to and including 30 November 2019. Data from Services Australia Complex Drugs aHUS monthly reports from January 2017 up to and including 30 June 2020 has also been used in this update. Analyses in the report include:

- New and prevalent patient counts by year
- Prescriptions by treatment phase
- Patient age at initiation
- Length of treatment
- Length of therapy pre and post February 2016 restriction change
- Length of treatment by top 3 initial prescribers
- Patient status
- Length of treatment using date of death data
- Prescriber type
- Initiating prescribers by prescriber type
- Patient count by provider
- Approved patient affected organs
- Restriction sequence

- Patient flow from 'Initial' to 'Balance of Initial'
- Approved patient vaccination / antibiotic evidence status

### ***Key Findings***

- Since its listing in December 2014, 323 patients have been supplied eculizumab for aHUS (to the end of May 2020). Of these 87 (27%) people were on treatment at the end of the analysis period; meaning 236 people had stopped treatment.
- DoD data shows that a total of 74 people out of 298 who were supplied eculizumab from December 2014 to 20 March 2020 had died. Of these 74, 39 (13.1% of total patient) have died whilst on treatment. This indicates that some patients may have been treated beyond disease progression.
- Adults (18 years and over) make up the majority (90.4%) of patients treated with eculizumab.
- Of the top 3 prescriber types (general practitioners (GPs), nephrologists and haematologists), patients prescribed initial treatment by nephrologists and haematologists spent the longest amount of time on treatment.
- At the time of initial application approvals, 68% of patients had an ADAMTS-13 score recorded and 32% did not. Of the patients without an ADAMTS-13 score, 29.9% did not proceed to receive further treatment. The remaining 70.1% provided an ADAMTS-13 score and proceeded to receive the balance of initial supply.
- There were changes to the restriction in 2016, which may have led to a decrease in LoT. These changes included the addition of having to provide extra information in the application i.e. serial haematological results every three months while on treatment; evidence of an identifiable genetic mutation, and prior history of aHUS.
- Restriction changes in January 2017 led to an increase in the number of adult patients. These changes included adding the possibility of eligibility for treatment when non-renal thrombotic microangiopathy (TMA) related organ damage is present and clarification that the progressing TMA must be caused by aHUS.
- Initiating and prevalent patient numbers are showing signs of stabilising with 2019 being the first year that total patient numbers did not increase compared to the previous years' total patient numbers.
- The rate of growth in PBS patients is showing signs of declining.

## Purpose of analysis

In September 2017, DUSC considered a 24 month predicted versus actual utilisation analysis of eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS). For details refer to the Public Release Document.

An update to the utilisation was conducted in February 2019, which examined an additional 12 months of data that was available, and included the number of initiating and prevalent patients, and the extent of continuation, stopping and restarting of therapy.

In considering the utilisation of eculizumab in February 2019, DUSC requested a further analysis to assess time on treatment after changes to the restriction, which enabled a new population to access the medication and to identify any discontinuation due to death. For details refer to the Public Release Document.

In its consideration of the February 2019 DUSC review, the Pharmaceutical Benefits Advisory Committee (PBAC) requested at its March 2019 meeting for DUSC to examine if differences in the time on therapy between patients was due to the prescribing patterns of individual clinicians.

## Background

### *Previous reviews by the DUSC*

This report does not replicate background information contained in the previous reports. For background information, refer to the 24-month and 36-month predicted versus actual utilisation analysis of eculizumab for aHUS Public Release Documents.

### *Restriction*

Abridged PBS restrictions of eculizumab for aHUS are available in [Appendix A](#). For details of the current PBS listing, including full restriction wording, refer to the PBS website.

### *Changes to listing*

A summary of the changes to the eculizumab PBS restrictions is available in [Appendix B](#). The changes to restriction wording were as a result of consultation with a clinical reference group.

### Summary of changes

- Clarified terminology and administrative arrangements to better target the patient group for whom PBAC had recommended eculizumab.
- Initial treatment period was extended from 12 to 24 months.
- Information provided by clinicians at the assessment period for continuing therapy was enhanced to include patient information on factors associated with an increased risk of recurrence and the likely clinical consequence of a recurrence. These include an identified genetic mutation, history of multiple episodes of aHUS

(either before commencing eculizumab treatment or following a treatment break), and history of kidney transplant.

- Additional requirements for data reporting were added at 18 and 24 months.
- All pre-existing patients were transitioned onto subsidised treatment; which meant the grandfather restriction could be removed.

Current PBS listing details are available from the PBS website.

## Methods

The analyses used data from:

- Services Australia supplied prescriptions database for dates of supply up to and including 31 May 2020; extracted 2 July 2020.
- Services Australia Authority Approval database, extracted 2 July 2020
- Services Australia – Complex Drugs (Tasmania) aHUS monthly reports from January 2017 up to and including June 2020.

The Services Australia supplied prescriptions database includes data submitted to Services Australia for payment of an R/PBS subsidy by the Government by all approved pharmacies in Australia. This dataset contains de-identified information that includes a unique patient identification number (PIN), dates and quantities of supply of all PBS listed drugs, including prescriber and pharmacy identification numbers.

The Authority Approval database contains information that is provided to Services Australia by prescribers to support approval for a PBS Authority Required prescription. De-identified information is recorded by PIN and can be matched to the prescriptions database.

The Service Australia aHUS monthly reports contain patient initiation and recommencement of treatment information.

Analyses in the report include:

- New and prevalent patient counts by year (Figure 1 and Table 1)
- Prescriptions by treatment phase (Figure 2)
- Patient age at initiation (Table 2)
- Length of treatment (Figure 3 and Table 3)
- Length of therapy pre and post February 2016 restriction change (Figure 4 and Table 4)
- Length of treatment by top 3 initial prescribers (Figure 5 and Table 5)
- Patient status (Table 6)
- Length of treatment using date of death data (Table 7 and Table 8)
- Prescriber type (Figure 6)
- Initiating prescribers by prescriber type (Figure 7)
- Patient count per prescribing provider (Table 9)
- Approved patient affected organs (Table 10)
- Restriction sequence (Table 11)

- Patient flow from 'Initial' to 'Balance of Initial' (Figure 8)
- Approved patient vaccination / antibiotic evidence status (Table 12)

### **Definitions**

A patient was defined as an initiator (or 'new patient') based on the date of first supply of PBS subsidised eculizumab. This group contained patients who were naïve to eculizumab and 'grandfathered' patients; i.e. patients who obtained eculizumab through other means (such as a sponsor run compassionate program) prior to listing on the PBS and then commenced PBS-subsidised treatment.

To count patients by treatment phase, data from the Services Australia supplied prescriptions database were merged with data from the Services Australia Authority approvals database. This allowed delineation of the patient's place in the continuum of therapy as described under the PBS item number restrictions.

Prescriber type was attributed to the de-identified prescriber number by Services Australia and was based on the major field of specialty, derived from the combination of the current registered specialty and the most Medicare services provided per quarter. Prescribers can work in several different specialties but are allocated by Services Australia to one major field of specialty per quarter.

The LoT analyses used the Kaplan Meier (aka Product-Limit) method. Two ways of measuring LOT were undertaken to account for patients stopping medicine for periods of time (called a 'break' in therapy). One analysis was inclusive of breaks in treatment and reported the total time on therapy. The second analysis was exclusive of treatment breaks and only reported the total time the patient received regular supplies of the medicine. A patient was deemed to have a break in treatment if the time between two of their supplied prescriptions was more than 3 times the median time to resupply (i.e.  $3 \times 28$  days), which is an estimated break in treatment of at least 2 times the median time to resupply.

A censoring definition was applied in the LoT analysis, to account for the end of the data observation period where patients who might be continuing supply appear to stop treatment (because there is no further data for supplies). A patient was deemed to be continuing treatment (classified as censored in the Product-Limit method) at the end of the data period (i.e. the end of May 2020) if their last prescription was within 3 times the median time to resupply of this end date. Otherwise, the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply.

As this analysis uses date of supply prescription data, there may be small differences in total number of supplies of eculizumab in the same period compared with publicly available Services Australia Medicare date of processing data.<sup>1</sup>

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<sup>1</sup> PBS statistics. Australian Government Services Australia. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>

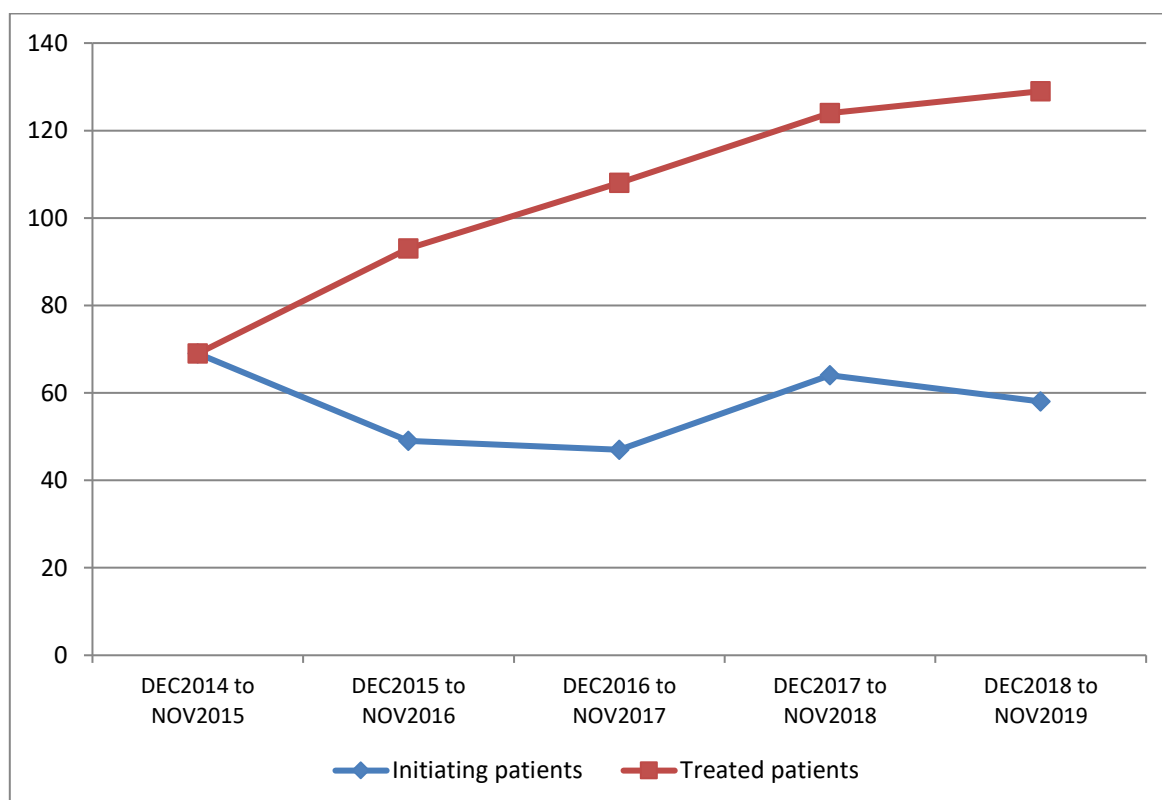
Date of death (DoD) data was sourced from Services Australia for all patients that had been treated with eculizumab up until the end of March 2020 (304 patients).

Additional analyses of length of eculizumab treatment used the DoD to adjust the coverage end date and the censoring status for patients who died on treatment. A patient was deemed to have died on treatment if their DoD was within one median time to resupply (i.e. 28 days) of their last supply of eculizumab. If this was the case then their medication coverage end date would shorten to their DoD. In addition the analysis was undertaken using two different censoring schemes. Initially the censoring was not adjusted, that is, a patient was not censored if they stopped treatment or died on treatment and censored if they were continuing treatment at the end of the data period (i.e. end of May 2020). A second “immortal world” censoring scheme was also used, that is, a patient was censored if they died on treatment or were continuing treatment at the end of the data period and not censored if they stopped treatment before death.

## Results

### Analysis of drug utilisation

#### Overall utilisation



**Figure 1: Initiating patients and total number of patients supplied eculizumab for aHUS**

Initiators are people supplied their first PBS-subsidised prescription.

Listing year is December to November.

Source: PIN count, Services Australia supplied prescriptions database to 30 November 2019; extracted 2 July 2020.

Figure 1 shows the total number of patients who were supplied eculizumab by listing year and of those patients how many received their first ever PBS supply of eculizumab in that listing year. These categories were determined from PBS supply data regardless of which restriction code (treatment phase) was used. Initiating patients include people receiving supply under the initial treatment restriction and the grandfather restriction. While grandfathered patients are continuing their eculizumab supply, they are considered new to PBS supply. The eculizumab listings include a range of treatment phases, summarised as initial, continuing, re-commencement (see Appendix A for further restriction details).

The number of patients supplied eculizumab has steadily increased since the time of listing, with 69 patients in Year 1, increasing to 187 patients from December 2018 to November 2019. It appears that the number of PBS patients per year may be steady, with figures for December 2017 to November 2018 being 188 patients. In total, 323 unique patients have been supplied eculizumab from the time of PBS listing (1 December 2014) to the most recent data (31 May 2020).

It was estimated that [REDACTED] patients would be supplied eculizumab. This was derived as:

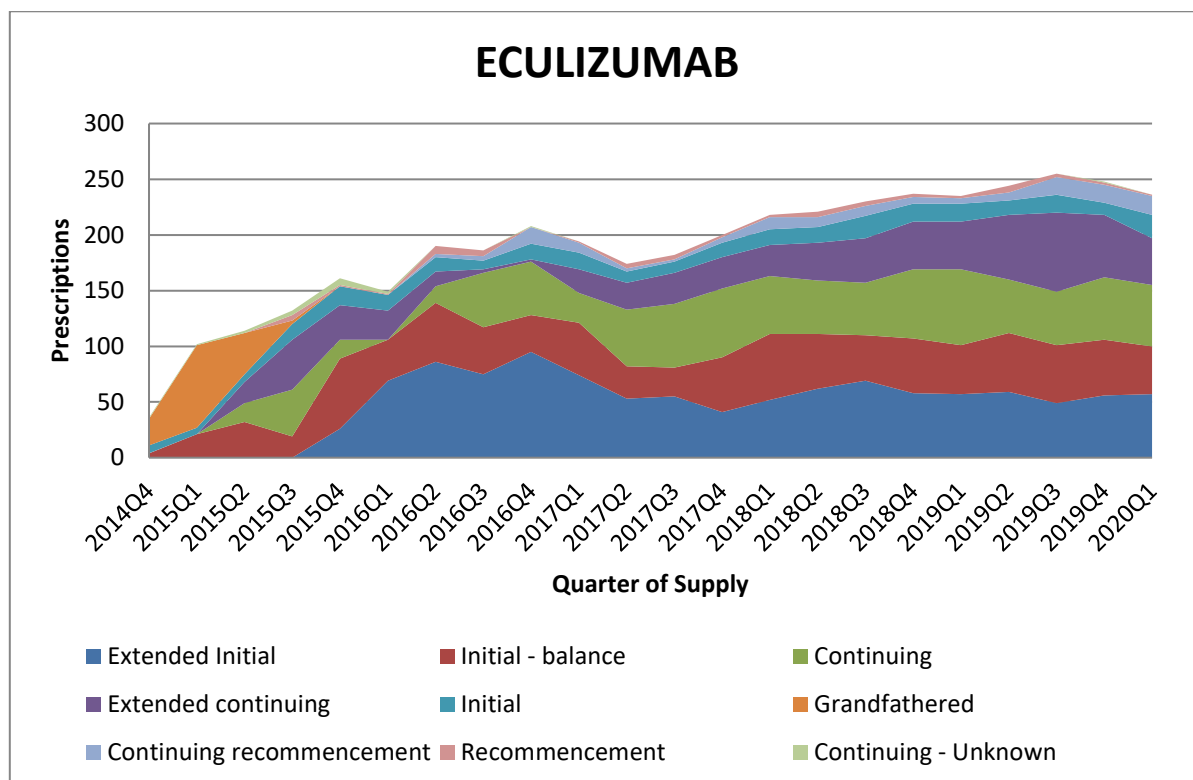
- Applying an aHUS prevalence of [REDACTED] persons per million (applied to the total Australian population of 26 million);
- Assuming [REDACTED] of aHUS patients would be diagnosed in 2019; and
- [REDACTED] of diagnosed patients would be supplied eculizumab.

**Table 1: Patients supplied eculizumab for the treatment of aHUS by year**

Year	PBS initiators	Re-initiating patients	Total PBS patients	% growth in PBS patients p.a.
2014	28		28	
2015	48		74	164%
2016	48		92	24%
2017	47	<5	107	16%
2018	64		126	18%
2019	56	<5	126	0%
Total	291	-	-	-

Source: PIN count, Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020. Initiators are people supplied their first PBS-subsidised prescription in that year.

Table 1 depicts the total number of patients and number of new patients by calendar year. 2019 was the first year that there has not been an increase in total patients compared to the previous year, since listing on the PBS.



**Figure 2: Prescriptions by treatment phase**

Source: Services Australia supplied prescriptions database and Authorities database to 31 May 2020; extracted 2 July 2020.

Figure 2 shows the number of eculizumab prescriptions supplied by quarter by the phase of treatment as per the Authorities database. Overall, the number of prescriptions supplied per quarter has increased over the period, from 102 in the first complete quarter (2015Q1) to 236 in the latest complete quarter (2020Q1). There has been a slight drop in 2020Q1, which is similar to the drop in the first quarter of other years. The data shows low rates of prescriptions attributed to recommencement, and continuing recommencement.

### Utilisation by age

**Table 2: Patient age at initiation**

	Initiating patients per year							
Age range	2014	2015	2016	2017	2018	2019	2020	Total
0-11 years	■	■	■	■	■	■	■	■
12-17 years	■	■	■	■	■	■	■	■
18+ years	■	■	■	■	■	■	■	■
Total	28	48	48	47	64	56	32	323

Time period: December 2014 – May 2020.

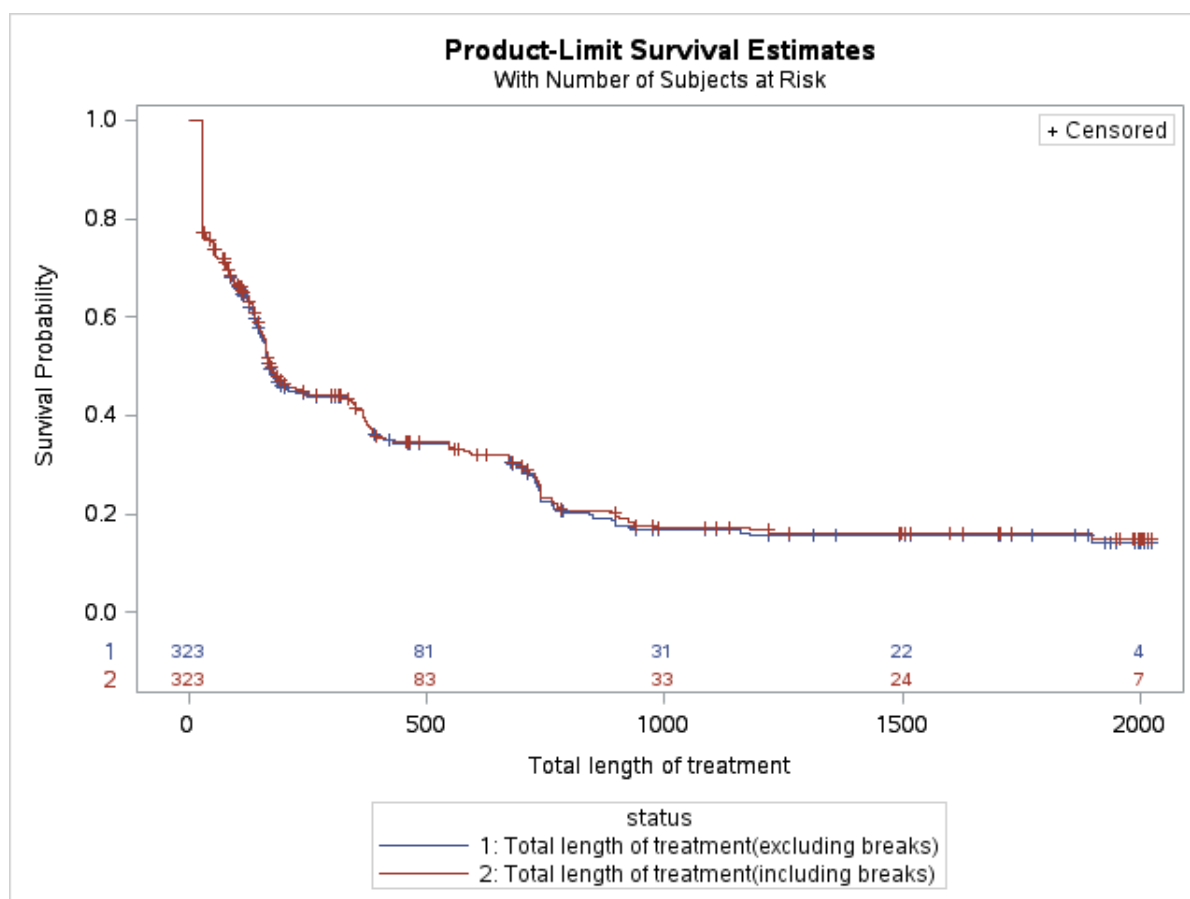
Source: PIN count, Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.



Table 2 shows that, from the time of listing to the most recent data, the proportion of adult patients (18 years and over) was 90%.

Since listing on the PBS paediatric patient numbers have held steady with an average of  $\leq 5$  patients per year, with the highest number of paediatric patients in the PBS listing year 2014. Adult patient numbers (18+) have doubled since PBS listing with a count of 24 in 2014 and an average of 48 per annum from 2015-2019. There is a noticeable increase in initiating adult patient numbers when comparing the average over years 2015-2017 (43) to 2018-2019 (56), this represents an increase of 30% in initiations over the time cohorts. This is probably due to the January 2017 restriction change, which added the following clause, to allow use “in recipients of a kidney transplant for end-stage kidney disease due to aHUS, a kidney biopsy confirming TMA”. This change allowed another population to access treatment and may have caused the increase in patient numbers. Despite initiations increasing, the duration of therapy count after the February 2016 restriction change has more than halved (as seen in Table 4).

### ***Duration of therapy***



**Figure 3: Length of treatment (days) at initiation analysis using the Product-Limit method**

Source: Services supplied prescriptions database to 31 May 2020 extracted 2 July 2020.

**Table 3: Length of treatment analysis descriptive statistics**

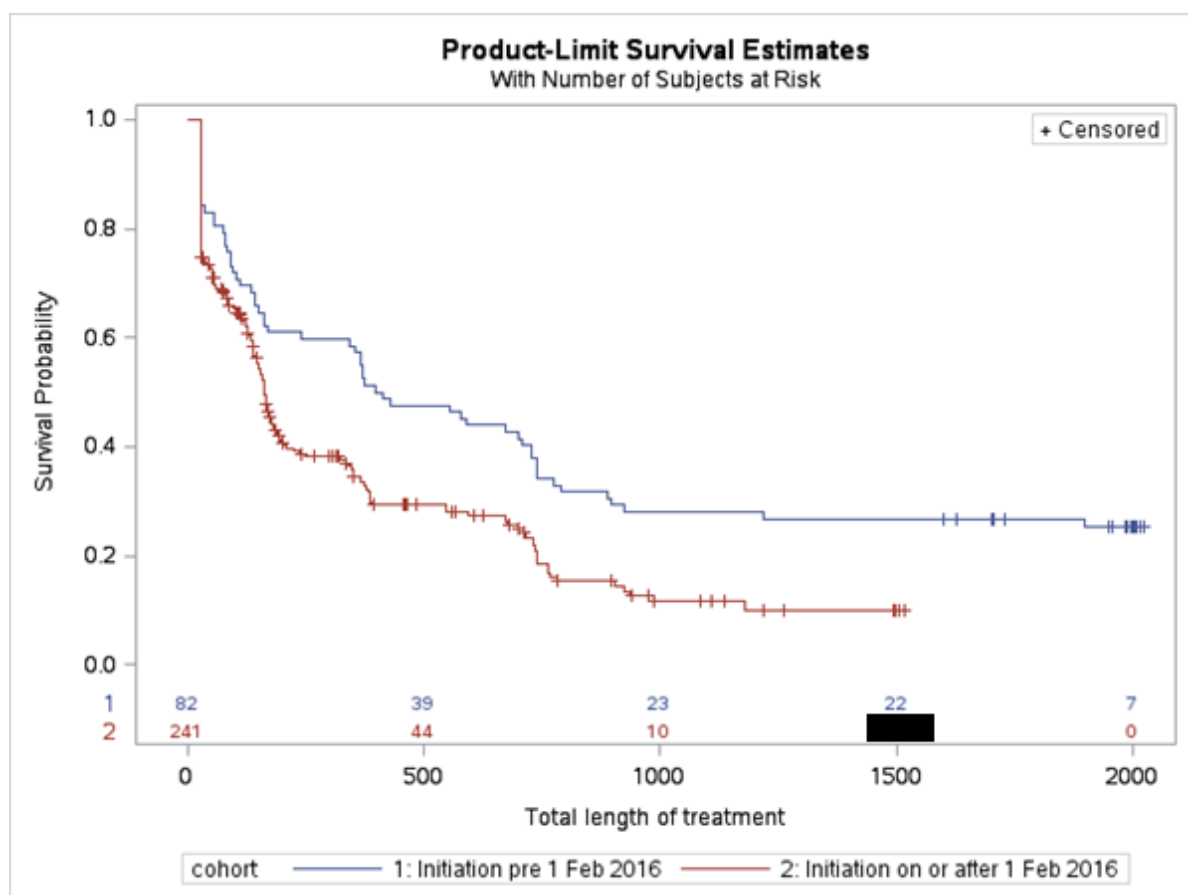
Length of treatment analysis	Mean	Median
Excluding breaks	412	323
Including breaks	420	335

Time period: December 2014 – May 2020.

Source: PIN count, Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

Figure 3 and Table 3 show the LoT. The total period of observation of prescriptions supplied was 1 December 2014 to 31 May 2020. Prescriptions supplied for all 323 patients were included.

At 31 May 2020, 87 people were deemed as continuing treatment and 236 were deemed to have finished treatment.



**Figure 4: Length of treatment (including breaks, days) pre and post February 2016 restriction change**

Source: Services Australia supplied prescriptions database to 31 May 2020 extracted 2 July 2020.

**Table 4: Length of treatment pre and post February 2016 restriction change**

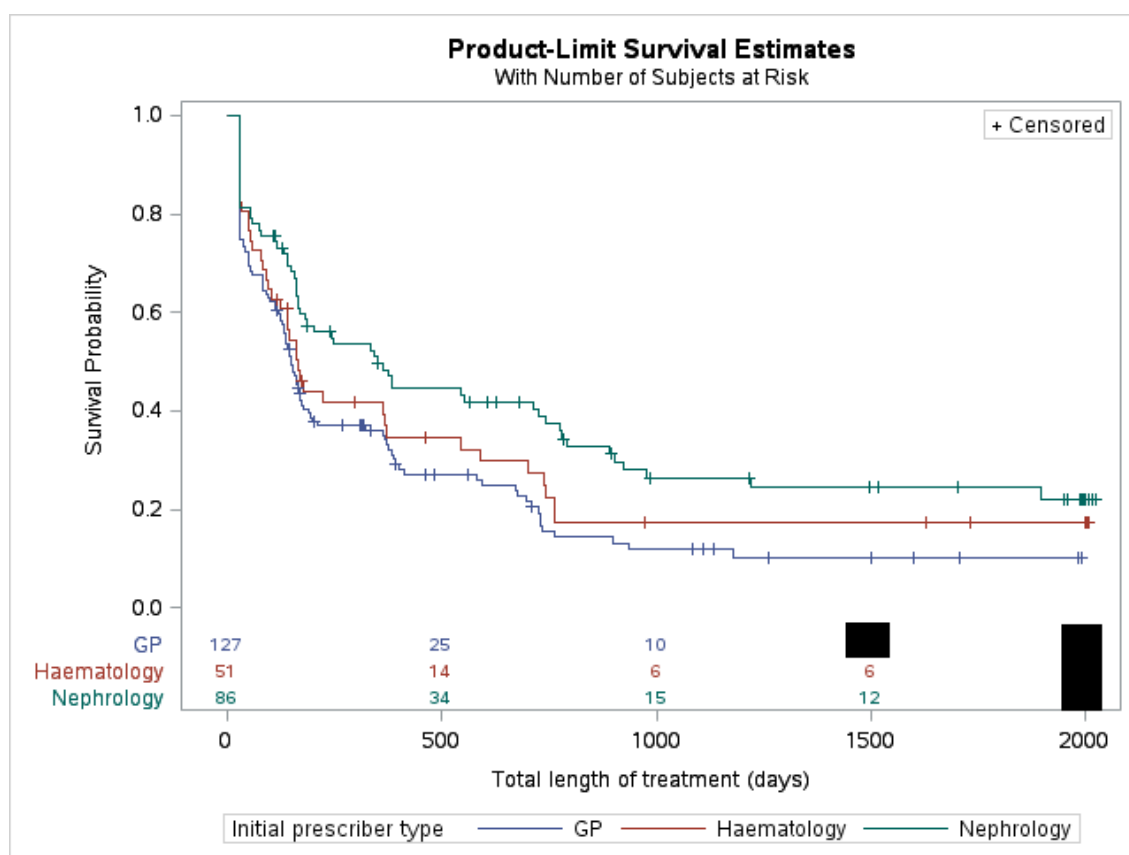
Cohort	Mean (days)	Median (days)
Initiation pre 1 Feb 2016	745	406
Initiation on or after 1 Feb 2016	359	161

Time period: December 2014 – May 2020.

Source: Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

Figure 4 shows the total LoT (including breaks) by cohorts, patients initiating treatment pre and post the restriction changes on 1 Feb 2016. The results in table Table 4 are for total LoT (including breaks). The results for “excluding breaks” have not been included as they are almost identical.

The data in Table 4 demonstrates that the February 2016 restriction to reduce LoT had the desired outcome, with a 48.2% reduction in the mean days of treatment and a 39.7% reduction on the median days of treatment. See Appendix B for a list of changes to eculizumab restrictions.



**Figure 5: Length of treatment (including breaks) by top 3 specialty types who prescribed initial treatment**

Source: Services Australia supplied prescriptions database to 31 May 2020 extracted 2 July 2020.

**Table 5: Length of treatment (including breaks) by top 3 initial prescriber types**

Initial prescriber type	Mean (days)	Median (days)
GP	343	150
Haematology	331	167
Nephrology	708	350

Time period: December 2014 – May 2020.

Source: Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

Figure 5 and Table 5 show that GPs provided the most initial prescriptions, while patients of nephrologists and haematologists were on treatment the longest. Further data analysis has shown that it is likely that almost all of the initiating GPs have provided these prescriptions in a hospital setting, more than likely in consultation with a specialist.

At 2000 days since initiation of treatment, no patients that had an initial GP prescription remained on treatment.

***Adjusting the estimate of Length of Treatment using Date of Death (DoD) data***

**Table 6: Treatment Status**

Treatment status	Patients	% patients
Alive and not on treatment	156	52.3%
Alive on treatment	68	22.8%
Died on treatment	39	13.1%
Died, but did not die on treatment	35	11.7%
Total	298	100%

Note: The data excludes 19 patients who were recent patients and had data outside of this data analysis period. DoD data is only complete until 31 December 2019 and partially complete until 20/3/2020. There is the possibility that some of the 224 alive patients might have died since the time this data was obtained.

Time period: December 2014 – 20 March 2020.

Source: PIN count, Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

During the time period (December 2014 to 31 May 2020) 74 (24.8%) of the 298 people who received eculizumab had died. This averages out to 4.1% per annum, and is less than the 1 year mortality rate of 13% using supportive care as reported by the TMA registry in the 2014 submission. Of these patients, 39 (13.1%) died whilst receiving eculizumab treatment. This may indicate that some patients were treated beyond disease progression, which is outside the PBS restriction.

**Table 7: Comparison of Length of treatment with and without adjustment for DoD (standard censoring)**

Length of treatment measure	Patients	Mean (days)	Median (days)
Total length of treatment (including breaks)	298	529.6	154
Total length of treatment (including breaks, adjusted for DoD)	298	527.5	151

Note: This table has been calculated using standard censoring where death whilst on treatment is a non-censored observation (i.e. patient is assumed to have ceased treatment at the DoD)

Time period: December 2014 – May 2020.

Source: PIN count, Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

**Table 8: Length of treatment adjusted for DoD and using “immortal world” censoring**

Length of treatment measure	Patients	Mean (days)	Median (days)
Total length of treatment (including breaks, adjusted for DoD)	298	611.5	183

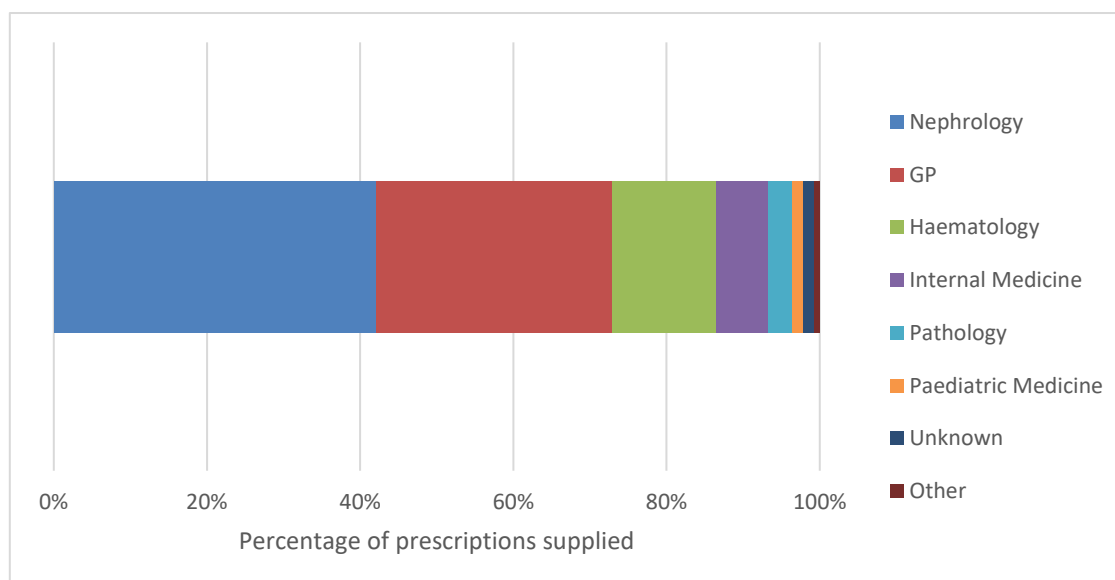
Note: This table has been calculated using “immortal world” censoring where death whilst on treatment is a censored observation (i.e. the patient is regarded as continuing treatment at the DoD) Death on treatment is defined if their DoD was within one median time to resupply (i.e. 28 days) of their last supply of eculizumab.

Time period: December 2014 – May 2020.

Source: PIN count, Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

If using the standard censoring model (Table 7) the DoD adjustment shows a slight decrease to the estimated LoT. Using the “immortal world” censoring model (Table 8) the DoD adjustment slightly increases the estimated LoT.

### Utilisation by prescriber type

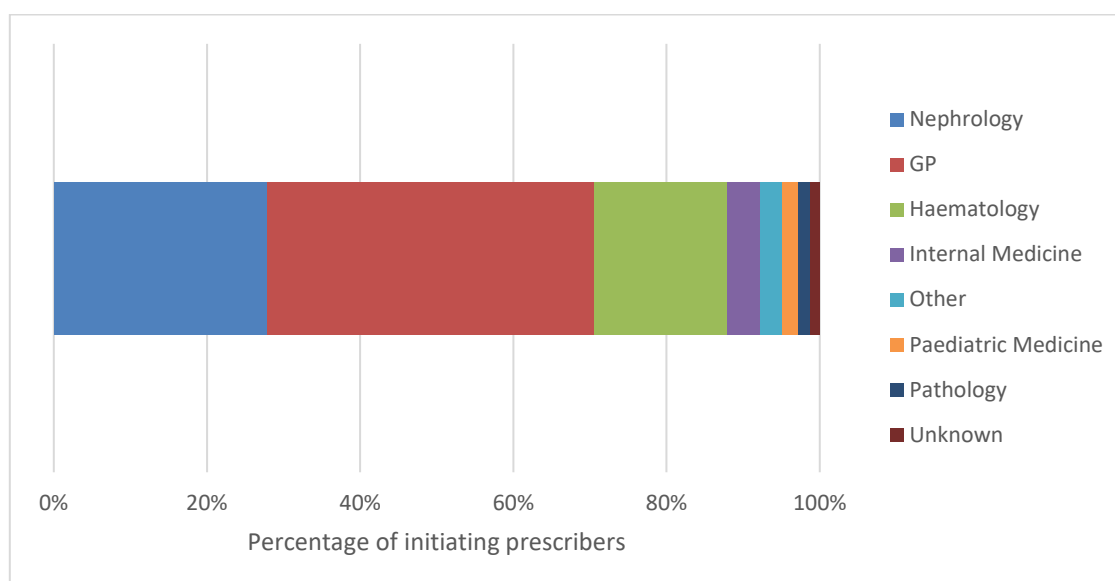


**Figure 6: Prescriptions supplied listing by prescriber type**

Data are presented as aggregate over the listing period. Other includes unknown, medical oncology, cardiology, immunology and respiratory specialties.

Source: Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

Figure 6 presents prescriptions by prescriber type over the PBS listing period to the most recent data available (December 2014 to May 2020). In this period, specialists wrote the majority of supplied prescriptions with nephrologists supplying the highest amount (1,818 prescriptions; 42% of prescriptions supplied). This was followed by GPs (1328 prescriptions; 31%) and haematologists (588 prescriptions; 14%). These results are similar to the previous reports. The restriction states that the patient 'Must be treated by a paediatric nephrologist, a nephrologist, a paediatric haematologist or a haematologist, or, must be in consultation with a paediatric nephrologist, a nephrologist, a paediatric haematologist or a haematologist.' Therefore, it is possible for non-specialist medical doctors (e.g. GPs) to prescribe eculizumab in consultation with the primary specialist managing the patient care.



**Figure 7: Initiating prescribers by prescriber type**

Data are presented as aggregate over the listing period. Other includes unknown, medical oncology, cardiology, immunology and respiratory specialties.

Source: Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

Figure 7 shows that GPs prescribe the majority of prescriptions (138 prescriptions; 43%) at the initiating stage, followed by nephrologists (90; 28%) and haematologists (56; 17%). As mentioned previously this is likely due to GPs writing prescriptions within a hospital setting in consultation with a specialist.

**Table 9: Patient count per prescribing provider**

Patients per prescribers	Initiating prescribers	PERCENT
1	189	76.8
2	44	17.9
3+	13	5.3
Total	246	100

Source: Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

The Services Australia supplied prescription database shows that there were 391 distinct prescribers that prescribed prescriptions for 323 patients, and 246 distinct prescribers that prescribed the initial prescription for these patients. Thus, there was on average less than 2 patients per initiating prescriber and 95% of initiating prescribers have had only 1 or 2 patients.

**Table 10: Approved aHUS patients affected organs**

Affected Organ	Patients	% Patients
Kidney	153	73.9%
Kidney;Other organ <sup>a</sup>	15	7.2%
Kidney;Neurological	12	5.8%
Kidney;Cardiac	8	3.9%
Kidney;Gastrointestinal	6	2.9%
Neurological	6	2.9%
Other <sup>b</sup>	7	3.4%
Total	207	100.0%

Note: 2 patients records in the report did not have any organ damage information recorded. This count has not been included in this table.

<sup>a</sup>Includes Kidney;Pulmonary, Kidney;Neurological;Gastrointestinal, Kidney;Neurological;Cardiac, Kidney;Neurological;Gastrointestinal;Pulmonary, Kidney;Neurological;Pulmonary, Kidney;Neurological;Cardiac; Gastrointestinal, Kidney;Cardiac;Gastrointestinal, and Kidney;Neurological;Cardiac;Pulmonary

<sup>b</sup> Includes gastrointestinal, neurological;cardiac, neurological;pulmonary, and pulmonary

Time period: January 2017 – June 2020.

Source: Services Australia Complex Drugs (Tasmania) aHUS monthly report January 2017 to 30 June 2020.

Source: Services Australia Complex Drugs (Tasmania) aHUS monthly report January 2017 to 30 June 2020.

Table 10 shows the breakdown of affected organs in applications for eculizumab. As expected the majority (97.1%) of approved applications note the kidney as an affected organ.

### **Utilisation by authority**

**Table 11: Restriction sequence - applications by restriction type**

Treatment phase sequence	Patients	% Patients
Initial -> Initial - balance	59	35.3%
Initial	48	28.7%
Initial -> Initial - balance -> Extended Initial	29	17.4%
Initial -> Initial - balance -> Extended Initial -> Continuing	25	15.0%
Other	6	3.6%
Grand Total	167	100.0%

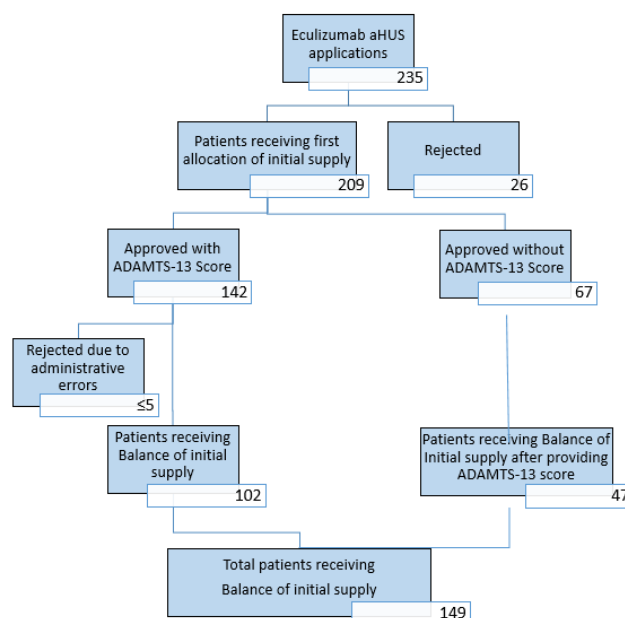
Time period: December 2017 – November 2019.

Source: PIN count, Services Australia supplied prescriptions database to 31 May 2020; extracted 2 July 2020.

The top four restriction sequences represent 96.4% of total initiators for eculizumab. Of the 167 patients that initiated in 2017 to 2019, only 48 patients received an initial eculizumab prescription and did not continue through to further treatment.

### Authorities linked claims data

### Patient flow from 'Initial' to 'Balance of Initial' approval



**Figure 8: Flow chart depicting timing and extent of ADAMTS-13 testing during the treatment approval process**

Time period: January 2017 – June 2020.

Source: Services Australia Complex Drugs (Tasmania) aHUS monthly report 2017 to 30 June 2020.

Of the 209 patients who were approved to receive initial therapy, 142 had a record of an ADAMTS-13 score. Of the 67 patients who were approved initial treatment without an ADAMTS-13 score, 47 patients had their ADAMTS-13 test score recorded when approved a Balance of Initial supply. All patients approved a Balance of Initial supply had an ADAMTS-13 score recorded.

A high proportion of patients can be found on extended continuing therapy. Based on the authorities data there were  $\leq 5$  rejected applications due to administrative errors. There were no cases of rejected applications due to clinical reasons in patients continuing with therapy after receiving an initial supply.



**Table 12: Approved patients vaccination / antibiotic evidence status**

Vaccination / Antibiotic Data	Patient count	Patient Count %
Antibiotics	41	19.6%
No	13	6.2%
Yes	155	74.2%
Total	209	100.0%

Time period: January 2017 – June 2020.

Source: Services Australia Complex Drugs (Tasmania) aHUS monthly report 2017 to 30 June 2020.

Amongst patients approved for treatment, evidence of vaccination for meningococcal was provided in most cases. However, there is no recorded vaccination information provided for 12 (5.7%) of the approved patients, despite this being a requirement under the restrictions.

## DUSC Consideration

DUSC recalled that at the time of first listing, the utilisation of eculizumab was considered to be highly uncertain due to the rarity of aHUS, the lack of reliable epidemiological data for the disease in Australia and the inconsistent use of diagnostic criteria to confirm aHUS from other conditions causing TMA.

DUSC noted that restriction changes implemented in February 2016 and January 2017 had a direct effect on the utilisation of eculizumab. The February 2016 restriction changes required further information on serial haematological results every three months while on treatment; evidence of an identifiable genetic mutation, and prior history of aHUS, there was a reduction. DUSC noted that these listing changes resulted in a reduction in the time on eculizumab, from a mean of 745 days before to 359 days after the changes. Further restriction changes implemented from January 2017 included eligibility for treatment when non-renal TMA related organ damage is present and clarification that the progressing TMA must be caused by aHUS. DUSC noted there was a noticeable increase in the number of initiating patients, particularly adults, following these listing changes.

DUSC considered that the analysis showed there was potential overprescribing for treatment beyond disease progression and in patients initiating treatment without an ADAMTS-13 score.

- DUSC noted that since listing in December 2014 to May 2020, there was a total of 323 patients supplied eculizumab under its aHUS restrictions. Of these patients, 73 percent (n=236) had stopped treatment including from 74 patient deaths in the period to March 2020. DUSC noted 39 patients died while on treatment which may indicate treatment beyond disease progression, which is outside the restriction. In its response to the review, the sponsor stated that as the analysis did not take cause of death into consideration, it cannot be conclusively stated that these patients were treated beyond disease progression. The sponsor further noted that death from TMA can be sudden.

- DUSC noted that 32 percent of patients did not have an ADAMTS-13 score recorded for their initial application, and of these patients, 30 percent did not apply for further treatment and their ADAMTS-13 status was therefore not verified. In its response, the sponsor argued that for patients who do not receive their balance of supply, the reason for their discontinuation of treatment cannot be determined from the available PBS administrative data. The sponsor further stated that the literature supports initiation to eculizumab based on predictive factors while waiting for ADAMTS-13 results, citing Schonermarck 2020 Clinical Kidney Journal, 2020; 13 (2): 208–216.

DUSC noted that while the number of initiating patients has increased, the growth in the number of prevalent patients had declined which was likely from patients having shorter treatment times since the February 2016 restriction changes. In its response, the sponsor stated that continued market growth in the longer-term could be expected based on the number of patients diagnosed and accessing eculizumab. The sponsor emphasised the need to retain the recommencement criteria in the restriction.

DUSC noted that based on the PBS data the number of re-initiating patients was low. The sponsor commented in its response that based on hospital orders, the number of re-initiating patients reported was below its supply numbers.

DUSC noted that general practitioners were identified as prescribing the majority of prescriptions at initiation. DUSC considered that it was likely that the GP prescribing was done in consultation with a specialist within a hospital setting.

## **DUSC Actions**

DUSC requested that the report be provided to the PBAC for consideration.

## **Context for analysis**

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

## **Sponsors' comments**

Alexion Pharmaceuticals Australasia Pty Ltd: The DUSC utilisation update shows that patients are benefiting from appropriate and effective arrangements that have been implemented to ensure rapid initiation of eculizumab to patients presenting with aHUS as a medical emergency.

## **Disclaimer**

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

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## Appendix A

**Table A1: abridged eculizumab restrictions (December 2018)**

<b>Condition:</b> aHUS	
<b>Treatment phase:</b> Initial treatment	
<b>Clinical criteria</b>	<ul style="list-style-type: none"> <li>• Patient must have active and progressing thrombotic microangiopathy (TMA) caused by aHUS, <b>AND</b></li> <li>• Patient must have ADAMTS-13 activity of greater than or equal to 10% on a blood sample taken prior to plasma exchange or infusion; or, if ADAMTS-13 activity was not collected prior to plasma exchange or infusion, patient must have platelet counts of greater than <math>30 \times 10^9/L</math> and a serum creatinine of greater than 150 mol/L, <b>AND</b></li> <li>• Patient must have a confirmed negative STEC (Shiga toxin-producing E.Coli) result if the patient has had diarrhoea in the preceding 14 days, <b>AND</b></li> <li>• Patient must have clinical features of active organ damage or impairment, <b>AND</b></li> <li>• Patient must not receive more than 4 weeks of treatment under this restriction.</li> </ul> <p>The restriction provides definitions for evidence of active and progressing TMA.</p>
<b>Treatment criteria</b>	Must be treated by a paediatric nephrologist, a nephrologist, a paediatric haematologist or a haematologist, or, must be in consultation with a paediatric nephrologist, a nephrologist, a paediatric haematologist or a haematologist.
<b>Treatment phase:</b> Initial treatment – balance of supply	
<b>Clinical criteria</b>	<ul style="list-style-type: none"> <li>• Patient must have received PBS-subsidised initial supply of eculizumab for this condition, <b>AND</b></li> <li>• Patient must have ADAMTS-13 activity of greater than or equal to 10% on a blood sample, <b>AND</b></li> <li>• Patient must not receive more than 20 weeks supply under this restriction.</li> </ul>
<b>Treatment Phase:</b> Extended initial treatment - Assessment phase	
<b>Clinical criteria</b>	<ul style="list-style-type: none"> <li>• Patient must have received treatment under the initial restriction with PBS subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must have demonstrated on-going treatment response of PBS-subsidised eculizumab treatment for this condition, <b>AND</b></li> <li>• Patient must not have experienced treatment failure with eculizumab including PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must not receive more than 56 weeks of treatment under this restriction.</li> </ul> <p>The restriction provides definitions of treatment response.</p>
<b>Treatment Phase:</b> Continuing treatment	
<b>Clinical criteria</b>	<ul style="list-style-type: none"> <li>• Patient must have received treatment under Extended Initial restriction with PBS subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must have demonstrated on-going treatment response of PBS-subsidised eculizumab treatment for this condition, <b>AND</b></li> <li>• Patient must not have experienced treatment failure with eculizumab including PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must not receive more than 24 weeks of treatment under this restriction.</li> </ul> <p>The restriction provides definitions of treatment response.</p>
<b>Treatment Phase:</b> Extended Continuing treatment	

<b>Condition: aHUS</b>	
<b>Clinical criteria</b>	<ul style="list-style-type: none"> <li>• Patient must have received treatment under the Continuing treatment with PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must have demonstrated on-going treatment response with PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must not have ever experienced treatment failure with eculizumab including PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must have a TMA-related cardiomyopathy as evidenced by left ventricular ejection fraction &lt; 40% on current objective measurement; <b>OR</b></li> <li>• Patient must have severe TMA-related neurological impairment; <b>OR</b></li> <li>• Patient must have severe TMA-related gastrointestinal impairment; <b>OR</b></li> <li>• Patient must have severe TMA-related pulmonary impairment on current objective measurement; <b>OR</b></li> <li>• Patient must have grade 4 or 5 chronic kidney disease (eGFR of less than 30 mL/min); <b>OR</b></li> <li>• Patient must have a high risk of aHUS recurrence in the short term in the absence of continued treatment with eculizumab, <b>AND</b></li> <li>• Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.</li> </ul> <p>The restriction provides definitions of treatment response.</p>
<b>Treatment Phase: Recommencement of treatment</b>	
<b>Clinical criteria</b>	<ul style="list-style-type: none"> <li>• Patient must have demonstrated treatment response to previous treatment with PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must not have ever experienced treatment failure with eculizumab including PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must have the following clinical conditions:(i) either significant haemolysis as measured by low/absent haptoglobin; or presence of schistocytes on the blood film; or lactate dehydrogenase (LDH) above normal; <b>AND</b>(ii) either platelet consumption as measured by either 25% decline from patient baseline or thrombocytopenia (platelet count &lt;150 x 10<sup>9</sup>/L);<b>OR</b>(iii) TMA-related organ impairment including on recent biopsy, <b>AND</b></li> <li>• Patient must not receive more than 24 weeks of treatment under this restriction.</li> </ul> <p>The restriction provides definitions of treatment response.</p>
<b>Treatment Phase: Continuing recommencement of treatment</b>	
<b>Clinical criteria</b>	<ul style="list-style-type: none"> <li>• Patient must have received treatment under Recommencement of treatment restriction with PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must have demonstrated ongoing treatment response to the previous 24 weeks of PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must not have experienced treatment failure with eculizumab including PBS-subsidised eculizumab for this condition, <b>AND</b></li> <li>• Patient must not receive more than 24 weeks of treatment under this restriction.</li> </ul> <p>The restriction provides definitions of treatment response.</p>

Source: PBS website. Current at August 2020.

## Appendix B

**Table B1: changes to eculizumab restrictions**

Date	Changes to restriction
<b>Initial</b>	
January 2016	Added: 'Serial haematological results (every 3 months while the patient is receiving treatment) must be provided with every subsequent application for treatment.'
January 2017	<p>Added clarification that:</p> <ul style="list-style-type: none"> <li>- the active and progressing TMA must be caused by aHUS.</li> <li>- where renal biopsy is used as evidence of a clinical feature of active TMA-related organ damage or impairment, the renal biopsy must be consistent with aHUS.</li> </ul> <p>Replaced: 'tissue biopsy confirming TMA in patients who do not have evidence of platelet consumption and haemolysis' with 'in recipients of a kidney transplant for end-stage kidney disease due to aHUS, a kidney biopsy confirming TMA.'</p> <p>Added: 'Claims of non-renal TMA-related organ damage should be made at the point of application for initial PBS-subsidised eculizumab (where possible), and should be supported by objective clinical measures. The prescriber's cover letter should establish that the observed organ damage is directly linked to active and progressing TMA, particularly when indirect causes such as severe thrombocytopenia, hypertension and acute renal failure are present at the time of the initial organ impairment.'</p> <p>Added that the written authority application:</p> <ul style="list-style-type: none"> <li>- must include 'a detailed cover letter from the prescriber.'</li> <li>- may include a statement that vaccination has or will be administered and appropriate antibiotic prophylaxis has been prescribed instead of a copy of a current Certificate of vaccination.</li> </ul>
<b>Initial – balance of supply</b>	
February 2016	Serial haematological results (every 3 months while the patient is receiving treatment) must be provided with every subsequent application for treatment.
January 2017	Restriction code change but no apparent change in restriction text.
<b>Extended Initial (listed November 2015)</b>	
November 2015	Restrictions for 'Continuing treatment - New patient' and 'Continuing treatment - following commencement of treatment after an initial 52-week period' introduced.
February 2016	<p>The two restrictions above were changed to 'Extended initial treatment – Assessment phase.'</p> <p>Removed specification of the number of weeks' therapy that the patient must have received under the initial restriction.</p> <p>'Patient must not receive more than 28 weeks of treatment per continuing treatment course authorised under this restriction,' changed to 'patient must not receive more than 56 weeks of treatment under this restriction.'</p>

Date	Changes to restriction
	<p>Added: 'A maximum of up to 56 weeks of treatment is allowed under this restriction, however an application must be submitted at 6 months, 12 months, 18 months and 24 months following commencing PBS-subsidised eculizumab. The authority application must include the following measures of response to the prior course of treatment, including serial haematological results (every 3 months while the patient is receiving treatment).'</p> <p>Additional information requested in the written application: '...An identified genetic mutation, if applicable; and A family history of aHUS, if applicable; and A history of multiple episodes of aHUS before commencing eculizumab treatment, if applicable; and A history of kidney transplant, if applicable, (especially if required due to aHUS); and An inclusion of the individual consequences of recurrent disease, if applicable...'</p> <p>Added: 'This assessment must be submitted no later than 4 weeks from the cessation of the prior treatment. Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with eculizumab.'</p>
January 2017	<p>Added that the written authority application:</p> <ul style="list-style-type: none"> <li>- must include 'a detailed cover letter from the prescriber.'</li> <li>- may include a statement that vaccination has or will be administered and appropriate antibiotic prophylaxis has been prescribed instead of a copy of a current Certificate of vaccination.</li> </ul>
<b>Continuing (listed December 2014)</b>	
February 2016	<p>Removed 'new patient' from continuing treatment</p> <p>Removed specification of the number of weeks' therapy that the patient must have received under the initial restriction.</p> <p>Removed 'per continuing treatment course authorised' from the maximum weeks of treatment.</p> <p>Added 'The authority application must include the following measures of response to the prior course of treatment...'</p> <p>Additional information requested in the written application: '...An identified genetic mutation, if applicable; and A family history of aHUS, if applicable; and A history of multiple episodes of aHUS before commencing eculizumab treatment, if applicable; and A history of kidney transplant, if applicable, (especially if required due to aHUS); and An inclusion of the individual consequences of recurrent disease, if applicable...'</p> <p>Added: 'This assessment must be submitted no later than 4 weeks from the cessation of the prior treatment. Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with eculizumab.'</p>
January 2017	<p>Added that the written authority application:</p> <ul style="list-style-type: none"> <li>- must include 'a detailed cover letter from the prescriber.'</li> <li>- may include a statement that vaccination has or will be administered and appropriate antibiotic prophylaxis has been prescribed instead of a copy of a current Certificate of vaccination.</li> </ul>
<b>Extended continuing (listed December 2014)</b>	

Date	Changes to restriction
November 2015	Changed from 'continuing treatment beyond initial 48 weeks of treatment' to 'continuing treatment beyond initial 52 weeks of treatment.'
February 2016	<p>Changed from 'continuing treatment beyond initial 52 weeks of treatment' to 'Extended Continuing treatment.'</p> <p>Added 'per continuing treatment course authorised' to the maximum weeks of treatment.</p> <p>Added 'The authority application must include the following measures of response to the prior course of treatment...'</p> <p>Rewording around timing requirements for haematological results.</p> <p>Additional information requested in the written application: '...An identified genetic mutation, if applicable; and A family history of aHUS, if applicable; and A history of multiple episodes of aHUS before commencing eculizumab treatment, if applicable; and A history of kidney transplant, if applicable, (especially if required due to aHUS); and An inclusion of the individual consequences of recurrent disease, if applicable...'</p> <p>Added: 'This assessment must be submitted no later than 4 weeks from the cessation of the prior treatment. Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with eculizumab.'</p>
January 2017	<p>Added that the left-ventricular ejection fraction and TMA-related pulmonary impairment must be based on current objective measurement</p> <p>Added 'high risk of aHUS recurrence in the short term in the absence of continued treatment with eculizumab' as an alternative clinical criterion to TMA-related cardiomyopathy, TMA-related neurological impairment, TMA-related pulmonary impairment, or chronic kidney disease.</p> <p>Added that the written authority application:</p> <ul style="list-style-type: none"> <li>- must include 'a detailed cover letter from the prescriber.'</li> <li>- may include a statement that vaccination has or will be administered and appropriate antibiotic prophylaxis has been prescribed instead of a copy of a current Certificate of vaccination.</li> </ul>
<b>Recommendation</b>	
November 2015	Changed from recommendation after 48 weeks to recommendation after 52 weeks
February 2016	<p>Changed from 'Initial 2 – recommendation' to 'Recommendation'</p> <p>Removed the time requirement (52 weeks) from the length of previous treatment.</p> <p>Added 'The authority application must include the following measures of response to the prior course of treatment...'</p> <p>Rewording around timing requirements for haematological results.</p> <p>Additional information requested in the written application: '...An identified genetic mutation, if applicable; and A family history of aHUS, if applicable; and A history of</p>



Date	Changes to restriction
	<p>multiple episodes of aHUS before commencing eculizumab treatment, if applicable; and A history of kidney transplant, if applicable, (especially if required due to aHUS); and An inclusion of the individual consequences of recurrent disease, if applicable...'</p> <p>Added: 'This assessment must be submitted no later than 4 weeks from the cessation of the prior treatment. Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with eculizumab.'</p>
January 2017	<p>Added that the written authority application:</p> <ul style="list-style-type: none"> <li>- must include 'a detailed cover letter from the prescriber.'</li> <li>- may include a statement that vaccination has or will be administered and appropriate antibiotic prophylaxis has been prescribed instead of a copy of a current Certificate of vaccination.</li> </ul>
<b>Continuing recommencement (listed December 2014)</b>	
February 2016	<p>Changed references to previous treatment under 'Initial 2 – recommencement' to 'Recommencement'</p> <p>Removed the time requirement (48 weeks) from the length of previous treatment.</p> <p>Added 'The authority application must include the following measures of response to the prior course of treatment...'</p> <p>Rewording around timing requirements for haematological results.</p> <p>Additional information requested in the written application: '...An identified genetic mutation, if applicable; and A family history of aHUS, if applicable; and A history of multiple episodes of aHUS before commencing eculizumab treatment, if applicable; and A history of kidney transplant, if applicable, (especially if required due to aHUS); and An inclusion of the individual consequences of recurrent disease, if applicable...'</p> <p>Added: 'This assessment must be submitted no later than 4 weeks from the cessation of the prior treatment. Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with eculizumab.'</p>
January 2017	<p>Added that the written authority application:</p> <ul style="list-style-type: none"> <li>- must include 'a detailed cover letter from the prescriber.'</li> <li>- may include a statement that vaccination has or will be administered and appropriate antibiotic prophylaxis has been prescribed instead of a copy of a current Certificate of vaccination.</li> </ul>
<b>Grandfathered</b>	
February 2016	<p>Changed from 'Initial 3 – grandfathered' to 'Grandfather'</p> <p>Changed references from 'Continuing treatment New Patient' to 'Extended Initial.'</p> <p>'Serial haematological results (every 3 months while the patient is receiving treatment) must be provided with every subsequent application for treatment. This will assist DHS in the consideration of the patient s eligibility for further PBS subsidised treatment' replaced with 'The authority application must include the following measures of response to the prior course of treatment, including serial haematological results (every 3 months while the patient is receiving treatment).'</p>

Date	Changes to restriction
	<p>Additional information requested in the written application: ‘...An identified genetic mutation, if applicable; and A family history of aHUS, if applicable; and A history of multiple episodes of aHUS before commencing eculizumab treatment, if applicable; and A history of kidney transplant, if applicable, (especially if required due to aHUS); and An inclusion of the individual consequences of recurrent disease, if applicable...’</p> <p>Added: ‘This assessment must be submitted no later than 4 weeks from the cessation of the prior treatment. Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with eculizumab.’</p>
January 2017	Grandfather restriction ceased.