

Eculizumab for aHUS: utilisation update

Drug utilisation sub-committee (DUSC)

February 2019

Abstract

Purpose

In September 2017, DUSC considered a 24 month predicted versus actual utilisation analysis of eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS). The committee requested a brief update on utilisation when an additional 12 months of data were available; including the number of initiating and prevalent patients, and the extent of continuation, stopping and restarting therapy.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

1 December 2014

Data Source / methodology

The analyses used data from the Department of Human Services (DHS) supplied prescriptions database for dates of supply up to and including 30 September 2018. Analyses in the report include:

- New and prevalent patient counts by year
- Prescriptions by treatment phase
- Patient age at initiation
- Hospital setting
- Prescriber type
- Length of treatment

Key Findings

- Since its listing in December 2014, 220 patients have been supplied eculizumab for aHUS (to September 2018). Of these 220 people,
 - 82 people were on treatment at the end of the analysis period (September 2018); meaning 138 people had stopped treatment.
 - 12 had a break (of more than 84 days) followed by a second treatment episode.
- In 2017, there were 109 patients supplied eculizumab; of whom 48 received their first PBS supply in 2017.
- The rate of growth in PBS patients has declined each year.

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](#). The committee requested a brief update on utilisation when an additional 12 months of data were available; including the number of initiating and prevalent patients, and the extent of continuation, stopping and restarting therapy.

Background

Previous reviews by the DUSC

This report does not replicate background information contained in the previous report. For background information, refer to the 24 month predicted versus actual utilisation analysis of eculizumab for aHUS [Public Release Document](#).

Methods

The analyses used data from the Department of Human Services (DHS) supplied prescriptions database for dates of supply up to and including 30 September 2018; extracted 19 November 2018. The DHS supplied prescriptions database includes data submitted to DHS 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, prescriber and pharmacy information. DHS also maintains the authority approval database. Prescribers provide necessary information to DHS to support approval for a PBS Authority Required prescription. De-identified information is recorded by PIN and can be matched to the prescriptions database.

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](#))
- [Hospital setting](#) (public or private) based on the pharmacy dispensing eculizumab
- [Prescriber type](#) (Figure 3)
- [Length of treatment](#) (Figure 4 and Table 3)

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

To count patients by treatment phase, data from the DHS supplied prescriptions database were merged with data from the DHS 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 approval number of the prescriber by the DHS 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 DHS to one major field of specialty per quarter.

The length of treatment analyses used the Kaplan Meier (aka Product-Limit) method. Two ways of measuring length of treatment were undertaken to account for patients stopping medicine for periods of time (called a 'break' in therapy). One analysis excluded the time of any breaks in treatment (i.e. reports the total time a patient is actually receiving regular supplies of the medicine) and the other did not. 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 x 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 length of treatment 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 September 2018) 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 Department of Human Services (DHS) Medicare date of processing data.¹

¹ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Results

Analysis of drug utilisation

Overall utilisation

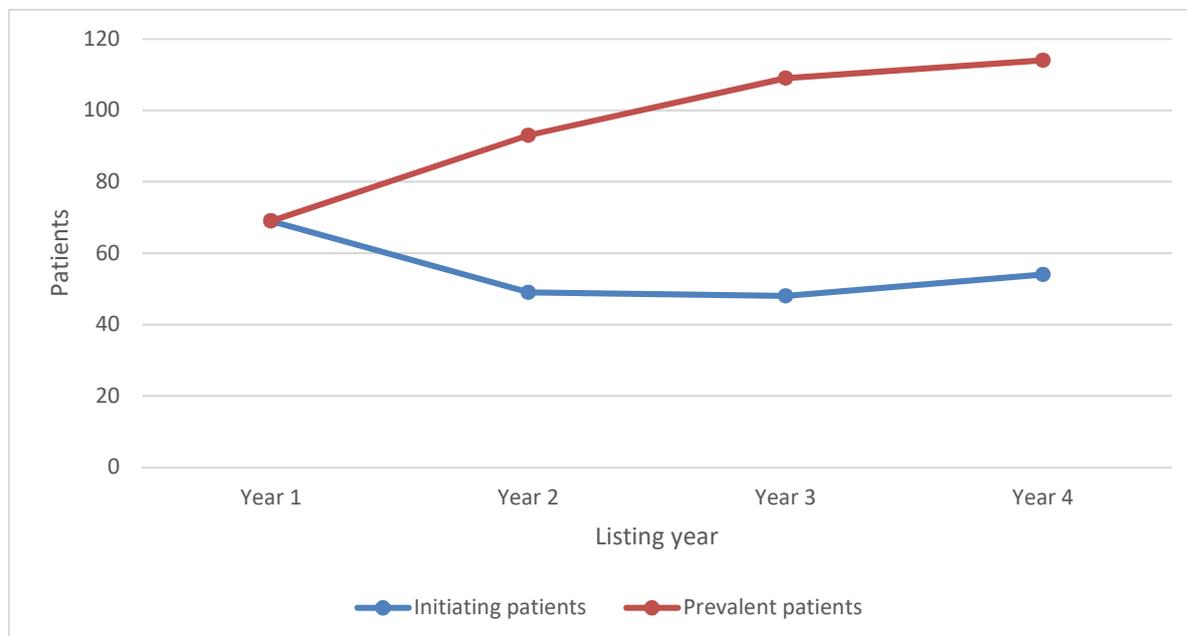


Figure 1: Initiating patients and total number of patients supplied eculizumab for aHUS

Initiators are people supplied their first PBS-subsidised prescription.

Listing year is December to November; year 4 is part-year to 30 September 2018.

Source: PIN count, DHS supplied prescriptions database to 30 September 2018; extracted 19 November 2018.

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 114 patients in the current listing year to date (10 months of data from December 2017 to September 2018 inclusive). While the current year to date is incomplete, it appears that the number of PBS patients per year may be steady. However, the number of initiating patients in the current listing year to date (54) has exceeded the numbers in listing years two and three (49 and 48 patients respectively), which had been stable. In total, 220 unique patients have been supplied eculizumab from the time of PBS listing (1 December 2014) to the most recent data (30 September 2018).

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

Year	PBS initiators	Total PBS patients	% growth in PBS patients p.a.
2014 (Dec only)	28	28	-
2015	48	74	164%
2016	48	92	24%
2017	48	109	18%
2018 (Jan-Sept inclusive)	48	110	1%
Total	220	-	-

Source: PIN count, DHS supplied prescriptions database to 30 September 2018; extracted 19 November 2018. 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. In 2017, 109 patients were supplied eculizumab under the aHUS restrictions. Of these patients, 48 (44%) received their first PBS-subsidised supply of eculizumab. While the number of PBS patients has increased each year, the rate of growth is decreasing (noting that data presented for 2018 is part-year).

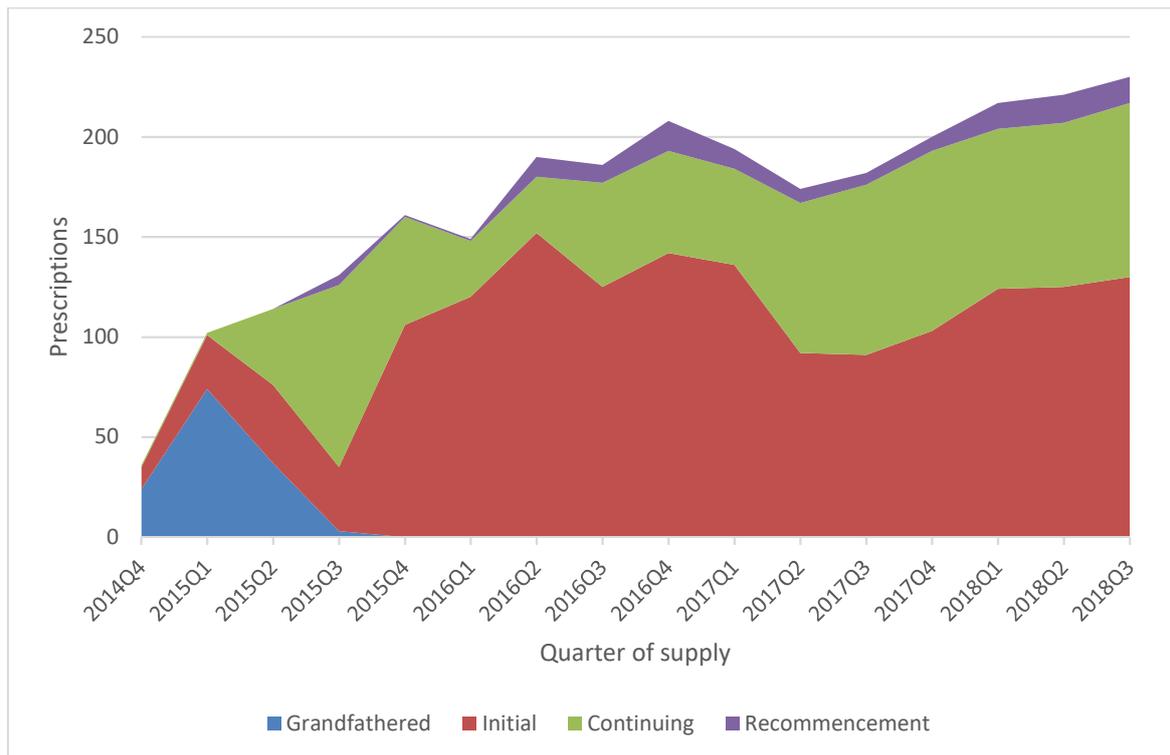


Figure 2: Prescriptions by treatment phase

Extended and balance of supply restrictions are included within these simplified treatment phases

Source: DHS supplied prescriptions database and Authorities database to 30 September 2018; extracted 19 November 2018.

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 230 in the latest complete quarter (2018Q3). Over the listing period to date, there have been 41 prescriptions supplied under the recommencement of treatment restriction (not including continuing recommencement).

Utilisation by age

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%. Data are presented as aggregate over the listing period rather than by year due to small patient numbers; however, the trend of paediatric to adult patients was similar in each year (proportion of adult patients ranged from 86-94%).

Table 2: Patient age at initiation

Age range	PBS initiators
0-11 years	14
12-17 years	9
18+ years	197
Total	220

Time period: December 2014 – September 2018.

Source: PIN count, DHS supplied prescriptions database to 30 September 2018; extracted 19 November 2018.

Utilisation by setting

The proportion of use by setting, based on dispensing pharmacy, was 86% public hospital and 14% private hospital over the period from listing (December 2014) to the most recently available data (September 2018). These proportions are equivalent to the previous analysis. The difference in cost between the public and private hospital prescriptions (currently \$47.29) is small as a proportion of the total cost per supply.

Utilisation by prescriber type

Figure 3 presents prescriptions by prescriber type over the PBS listing period to the most recent data available (December 2014 to September 2018). In this period, the specialty that prescribed the highest number of supplied prescriptions was nephrologists (1,176 prescriptions; 44% of prescriptions supplied). This was followed by general practitioners (753 prescriptions; 28%) and haematologists (396 prescriptions; 15%). Specialists wrote the majority of supplied prescriptions. These results are similar to the previous report. 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. general practitioners) to prescribe eculizumab in consultation with the primary specialist managing the patient care.

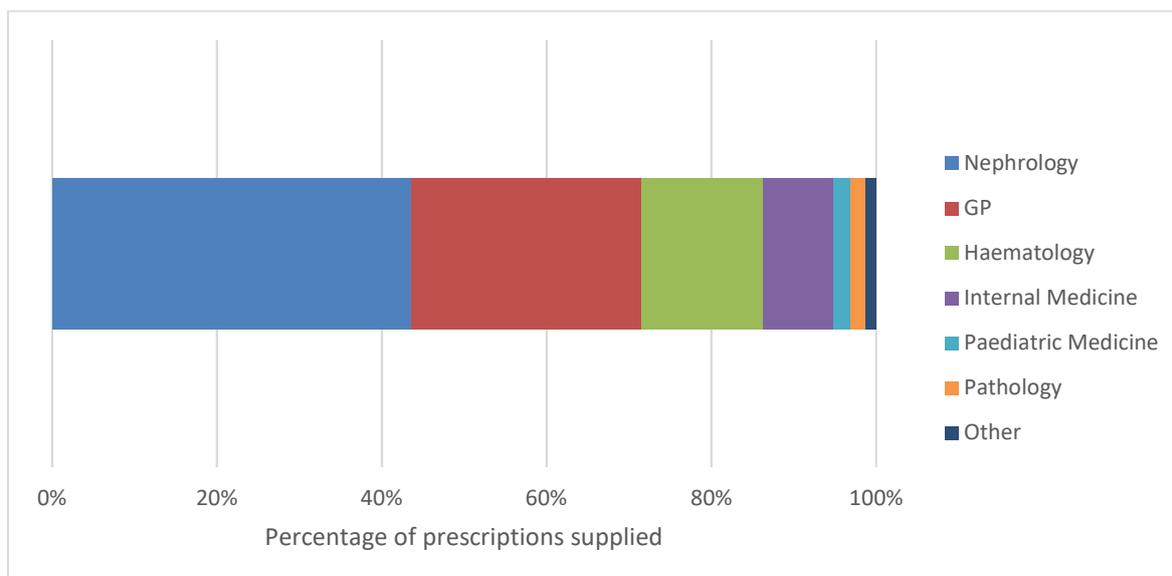


Figure 3: Prescriptions supplied listing by prescriber type

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

Source: DHS supplied prescriptions database to 30 September 2018; extracted 19 November 2018.

Duration of therapy

Figure 4 depicts the length of treatment analysis. The total period of observation of prescriptions supplied was 1 December 2014 to 30 September 2018. Prescriptions supplied for all 220 patients were included.

Under the definition that allows for right censoring, 82 people were deemed as continuing treatment at the end of the data period (i.e. end of September 2018) and 138 were deemed to have finished treatment. There were 12 people deemed to have had a break followed by a second treatment episode. There were no instances of people with two breaks and three episodes. Fifteen people were treated for at least 1,250 days (i.e. 3.4 years, where the period of listing to the most recent data was approximately 3.8 years). The mean and median duration of treatment with and without breaks are presented in Table 4.

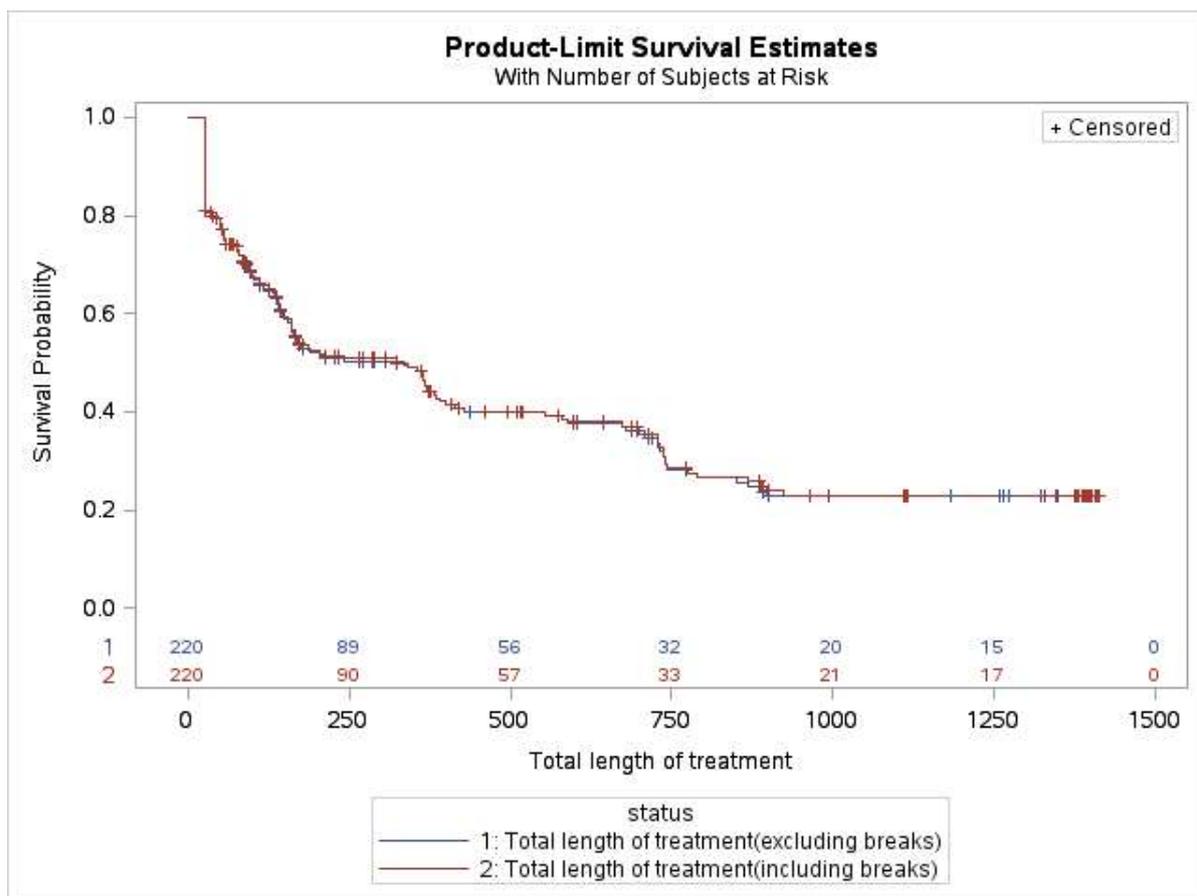


Figure 4: Length of treatment analysis using the Product-Limit method

Source: DHS supplied prescriptions database to 30 September 2018; extracted 19 November 2018.

Table 3: Length of treatment analysis descriptive statistics

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

Discussion and DUSC consideration

In the September 2017 report of eculizumab use, it was unclear whether the patient numbers were starting to plateau or would continue to rise. DUSC noted that the current report demonstrates that the rate of growth in PBS patients has declined in each year and appears to be plateauing (although the current year of data is incomplete). The number of prescriptions supplied has increased gradually over time and does not appear to have plateaued. In its response, the sponsor suggested that growth would continue. The sponsor presented prescription data by date of processing from the online Medicare PBS statistics to show an alternative growth rate. DUSC considered that date of supply data is a more appropriate measure of actual use, since processing is an administrative measure.

The length of treatment analysis indicated that few patients have a break in eculizumab treatment. It is not possible to obtain the reason for any discontinuation of supply from the available data. DUSC noted the length of treatment analysis also showed that there are key milestone steps visible in the chart that align with the various restriction stages. DUSC suggested that future analyses could show length of treatment by these milestones.

DUSC actions

- DUSC requested that the report be provided to the PBAC for noting.
- DUSC requested that the PBAC consider the request from the sponsor regarding separate item codes for recommencement and continuing prescriptions.
- DUSC considered that it was still appropriate to proceed with a further report on eculizumab use in 2020.

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

The Sponsor notes the comments by DUSC and PBAC and suggests they reconsider the request to separate the reporting of recommencement scripts from continuation scripts. This would enable a greater understanding of TMA recurrence rates in Australia and help inform best patient management.

Appendix A

Table A1: abridged eculizumab restrictions (December 2018)

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

Condition: aHUS	
Clinical criteria	<ul style="list-style-type: none"> • Patient must have received treatment under the Continuing treatment with PBS-subsidised eculizumab for this condition, AND • Patient must have demonstrated on-going treatment response with PBS-subsidised eculizumab for this condition, AND • Patient must not have ever experienced treatment failure with eculizumab including PBS-subsidised eculizumab for this condition, AND • Patient must have a TMA-related cardiomyopathy as evidenced by left ventricular ejection fraction < 40% on current objective measurement; OR • Patient must have severe TMA-related neurological impairment; OR • Patient must have severe TMA-related gastrointestinal impairment; OR • Patient must have severe TMA-related pulmonary impairment on current objective measurement; OR • Patient must have grade 4 or 5 chronic kidney disease (eGFR of less than 30 mL/min); OR • Patient must have a high risk of aHUS recurrence in the short term in the absence of continued treatment with eculizumab, AND • Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction. <p>The restriction provides definitions of treatment response.</p>
Treatment Phase: Recommencement of treatment	
Clinical criteria	<ul style="list-style-type: none"> • Patient must have demonstrated treatment response to previous treatment with PBS-subsidised eculizumab for this condition, AND • Patient must not have ever experienced treatment failure with eculizumab including PBS-subsidised eculizumab for this condition, AND • 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; AND(ii) either platelet consumption as measured by either 25% decline from patient baseline or thrombocytopenia (platelet count <150 x 10⁹/L);OR(iii) TMA-related organ impairment including on recent biopsy, AND • Patient must not receive more than 24 weeks of treatment under this restriction. <p>The restriction provides definitions of treatment response.</p>
Treatment Phase: Continuing recommencement of treatment	
Clinical criteria	<ul style="list-style-type: none"> • Patient must have received treatment under Recommencement of treatment restriction with PBS-subsidised eculizumab for this condition, AND • Patient must have demonstrated ongoing treatment response to the previous 24 weeks of PBS-subsidised eculizumab for this condition, AND • Patient must not have experienced treatment failure with eculizumab including PBS-subsidised eculizumab for this condition, AND • Patient must not receive more than 24 weeks of treatment under this restriction. <p>The restriction provides definitions of treatment response.</p>

Source: [PBS website](#). Current at December 2018.

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.

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