Eculizumab for aHUS: 24 month predicted versus actual analysis

# Drug utilisation sub-committee (DUSC)

## September 2017

### Abstract

## Purpose

To report on the use of eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS), including a routine 24-month predicted versus actual utilisation analysis.

## 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 31 May 2017. Analyses in the report include:

* Count of patients supplied eculizumab by quarter
* New and continuing patient counts by year
* Patient age at initiation
* Patient counts by treatment phase
* Hospital setting
* Prescriber type
* Length of treatment
* A predicted versus actual utilisation analysis for the first two years of listing.

## Key Findings

* Use of eculizumab for aHUS in terms of the number of patients, vials and expenditure was more than double what was predicted in both the first and second years of listing.
* Since its listing in December 2014, 145 patients have been supplied eculizumab for aHUS at a cost to Government of $71.5 million (to May 2017).

#### Purpose of analysis

To report on the use of eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS), including a routine 24-month predicted versus actual utilisation analysis.

#### Background

### Pharmacology

Eculizumab is a monoclonal antibody directed against the C5 complement protein[[1]](#endnote-1); part of the innate immune system that promotes inflammation and cell destruction. In aHUS, impaired regulation of complement activity leads to the formation of blood clots in small blood vessels throughout the body and severe inflammation of blood vessels.[[2]](#endnote-2) This can damage vital organs such as the kidneys, brain and heart. Eculizumab works by blocking the body’s inflammatory immune response, preventing blood clot formation and the destruction of the body’s own vulnerable blood and kidney cells.[[3]](#endnote-3)

### Therapeutic Goods Administration (TGA) approved indications

Eculizumab is indicated for the treatment of patients with:

* paroxysmal nocturnal haemoglobinuria (PNH) to reduce haemolysis.
* aHUS.

The Australian Approved Product Information contains a warning that eculizumab increases the risk of meningococcal infections and recommendations for vaccination and monitoring.

### Dosage and administration1

Patients must be administered a meningococcal vaccine prior to, or at the time of initiation of, eculizumab therapy.

## Adult patients

The aHUS dosing regimen for adult patients (≥ 18 years of age) consists of a 4-week initial phase followed by a maintenance phase:

* Initial phase: 900 mg of eculizumab via a 25 - 45 minute intravenous infusion every week for the first 4 weeks.
* Maintenance phase: 1200 mg of eculizumab administered via a 25 - 45 minute intravenous infusion for the fifth week, followed by 1200 mg of eculizumab administered via a 25 ‑ 45 minute intravenous infusion every 14 ± 2 days.

***Paediatric patients (< 18 years of age)***

Paediatric aHUS patients with body weight ≥ 40 kg are treated with the adult dosing recommendations above.

For paediatric aHUS patients with a body weight below 40 kg, the dosing regimen consists of:

| Patient Body Weight | Initial Phase | Maintenance Phase |
| --- | --- | --- |
| 30 to <40 kg | 600 mg weekly x 2 | 900 mg at week 3; then 900 mg every 2 weeks |
| 20 to <30 kg | 600 mg weekly x 2 | 600 mg at week 3; then 600 mg every 2 weeks |
| 10 to <20 kg | 600 mg weekly x 1 | 300 mg at week 2; then 300 mg every 2 weeks |
| 5 to <10 kg | 300 mg weekly x 1 | 300 mg at week 2; then 300 mg every 3 weeks |

aHUS patients should be monitored for signs and symptoms of thrombotic microangiopathy (TMA). Treatment is recommended to continue for the patient’s lifetime, unless discontinuation is clinically indicated.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

### Clinical situation

aHUS is a rare, chronic disease; with some patients experiencing recurrent episodes.[[4]](#endnote-4),[[5]](#endnote-5) A genetic basis for the disease can only be established in some patients; with some of these patients having both a genetic mutation and symptoms triggered by an environmental cause (e.g. infection, vaccinations, or pregnancy).5,[[6]](#endnote-6) The prognosis of aHUS is usually poor and is affected by the type of genetic mutation, if present.4,7 Clinical aHUS does not necessarily develop in all patients with a genetic mutation.

aHUS is diagnosed by clinical features and laboratory tests; and by the exclusion of thrombotic thrombocytopenic purpura (TTP) and other causes of HUS (e.g. infection).6 The PBAC considered aHUS to be a severe disease, associated with high risk of end stage renal failure and mortality, particularly at its first presentation.5 The PBAC considered that there is a high clinical need for an effective treatment for aHUS, particularly acute events.

Data on aHUS epidemiology, incidence and prevalence are limited.4 The PBAC noted that the submission estimated that the prevalence of aHUS is 3.3 to 7 cases per million.5

Plasma therapy, either with regular infusions of fresh frozen plasma and or plasma exchange, was traditionally first-line treatment for aHUS.6,[[7]](#endnote-7) Plasma therapy continues to have a place in therapy even when eculizumab is available for treatment. Plasma therapy may be started while awaiting the results of diagnostic tests to confirm aHUS and hence eculizumab suitability.6

Additional treatment options for aHUS include renal transplant, liver transplant, or combined liver-kidney transplant.6 Renal transplant is associated with a very high incidence of recurrent aHUS and graft loss despite the use of plasma therapy. Liver transplant alone or combined liver-kidney transplants have been used successfully in patients with aHUS. While combined liver-kidney transplantation has been associated with a poor outcome as a result of premature liver failure, concurrent treatment with eculizumab may reduce this risk. Liver-kidney transplantation should not be carried out without a preparative regimen such as plasma therapy or eculizumab.

### PBS listing details

Eculizumab for the treatment of aHUS was PBS-listed on 1 December 2014. Written applications for authority to prescribe must be submitted to the Department of Human Services (DHS). Table 1 provides the PBS listing details as at August 2017.

Table 1: PBS listing of eculizumab for atypical haemolytic uraemic syndrome

| Phase | Item | Name, form & strength, pack size | Max. qty. packs | Max. qty. units | Rpts | DPMQ | Brand name and manufacturer |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **S100 HSD Private** | | | | | | | |
| Initial | 10182X | ECULIZUMAB  300 mg/30 mL injection, 30 mL vial | 1 | 1 | 0 | $5984.65 | Soliris®  Alexion Pharmaceuticals Australasia Pty Ltd |
| Initial – balance | 10192K | 1 | 1 | 4 | $5984.65 |
| Extended initial | 10521R | 1 | 1 | 6 | $5984.65 |
| Continuing and re-commencement | 10194M | 1 | 1 | 5 | $5984.65 |
| **S100 HSD Public** | | | | | | | |
| Initial | 10191J | ECULIZUMAB  300 mg/30 mL injection, 30 mL vial | 1 | 1 | 0 | $5937.50 | Soliris®  Alexion Pharmaceuticals Australasia Pty Ltd |
| Initial – balance | 10190H | 1 | 1 | 4 | $5937.50 |
| Extended initial | 10525Y | 1 | 1 | 6 | $5937.50 |
| Continuing and re-commencement | 10183Y | 1 | 1 | 5 | $5937.50 |

S100 = section 100. HSD = Highly Specialised Drug. Source: the PBS website. Current at August 2017.

## 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. These restriction changes clarified terminology and administrative arrangements to better target the patient group for whom PBAC had recommended eculizumab. The initial treatment period was extended from 12 to 24 months. The 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; thus the grandfather restriction was removed.

Current PBS listing details are available from the PBS website.

### Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

Eculizumab for the treatment of aHUS was considered for PBS listing at three PBAC meetings. For further details refer to the Public Summary Documents from the March 2013 PBAC meeting, March 2014 PBAC meeting and August 2014 PBAC meeting.

The PBAC was satisfied that eculizumab provides, for some patients, a significant improvement in efficacy over supportive care; that is, for patients with active, progressive TMA during acute episodes of aHUS and who have not progressed to end stage renal disease (ESRD) i.e. greater than four months on dialysis; or for prevalent patients on chronic dialysis demonstrating extra-renal TMA. The PBAC considered that the structure and inputs of the economic model did not capture the full benefits of eculizumab treatment in this disease, and concluded that eculizumab would be likely to be cost effective in patients who achieve a complete response to treatment.

At its July 2017 meeting, the PBAC recommended extending the listing of eculizumab for the prevention of aHUS in patients at moderate-high risk of recurrence who have received a renal allograft for ESRD due to aHUS, irrespective of whether they have previously been successfully treated with eculizumab for aHUS.[[8]](#endnote-8)

Eculizumab is also available through the Life Saving Drugs Program for eligible patients with PNH.

## Epidemiology and patient numbers

The likely number of patients treated per year was estimated to be less than 100 patients in Year 5. The PBAC agreed that the estimates are highly sensitive to any small change in patient numbers due to the high acquisition cost of eculizumab.

## Dose

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.

## Duration and Continuation

PBAC considered that there was no convincing evidence to support the view that all patients should routinely have uninterrupted, life-long eculizumab therapy. This lack of evidence was recorded in the draft stakeholder meeting outcome statement: “All agreed that long-term data on the optimal dose and duration of treatment with eculizumab for patients with aHUS are lacking.” In the absence of long-term data and with the potential for harms with long term use, some of which are already known, the PBAC re-iterated its advice from earlier considerations of submissions for eculizumab in aHUS. The PBAC advised that where patients are able to demonstrate a response to the point that they achieve remission, it would be reasonable for PBS-subsidised treatment to discontinue after [a defined period] given that eculizumab is not without side effects. PBAC noted that the clinical progress of these patients would be monitored and the need for further treatment with eculizumab assessed as part of usual care.

The PBAC noted that there is no strong clinical rationale to support a particular

time-frame for the initial period of eculizumab. The initial time frame for treatment was 12 months. This has been extended to 24 months following further consultation with clinicians experienced in treatment of patients with aHUS (refer to Changes to listing section above).

## Cost

The submission (March 2013) assumed a treatment rate of approximately 50 percent of patients diagnosed with aHUS. This remained constant in each submission. There was no justification provided to explain the estimated treatment rate; and in PBAC’s view, the figure is likely to be higher than this, leading to an increase in the total cost.

The re-submission (PBAC March 2014) estimated a total cost to the PBS of between $100 million and $150 million over the first five years of listing (based on updated Australian population estimates). The previous submission estimated the cost to be higher, while within the same range.

The PBAC considered that the net cost per year for the PBS remained highly uncertain given the lack of reliable data on the prevalence and incidence of aHUS in Australia, the rarity of the condition and inconsistent use of diagnostic criteria in the past.

## Risk of use beyond the requested restriction

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.

The diagnosis of aHUS is confirmed in clinical practice by exclusion of other conditions causing TMA, which include Shiga-toxin E.coli (STEC) infection, thrombotic thrombocytopaenic purpura (TTP), malignancy, HIV or common drugs associated with inducing TMA. The treatment algorithm for aHUS proposed by the sponsor stated that, at diagnosis, the ADAMTS-13 and STEC tests will be used to exclude diagnosis of TMA due to STEC infection and TTP respectively. 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.

The PBAC in March 2014 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. This view was not altered in later considerations.

## Consumer input and clinical need

Treatment with eculizumab costs between $200,000 and $500,000 per patient per year. The PBAC acknowledged the strong consumer support for subsidised access to eculizumab in aHUS.

The PBAC considered aHUS to be a severe disease, associated with high risk of end stage renal failure and mortality, particularly at its first presentation. The PBAC considered that there is a high clinical need for an effective treatment for aHUS, particularly acute events.

The PBAC noted that all the eculizumab studies showed that aHUS patients treated with eculizumab experienced a significant improvement in TMA response, haematological normalisation, kidney function and quality of life compared to baseline.

## Recommendation

The PBAC considered that eculizumab would be cost-effective at a price justified by the existing evidence and if the measures discussed below were implemented to contain risks associated with the cost of the drug to the PBS:

* the sponsor should rebate the Commonwealth the price of eculizumab provided to patients who do not achieve a complete remission to treatment;
* under a managed entry scheme, the sponsor agrees to:

(i) price rebates commensurate with the magnitude of the clinical response achieved;

(ii) fund a structured program to collect evidence aimed at resolving the identified areas of uncertainty, including treatment breaks for those patients who have achieved complete remission;

(iii) develop with the PBAC cessation of treatment criteria for patients not achieving a complete response, including definition of an adequate duration of a trial of treatment;

* 100% rebate over the financial estimates in the submission.
* the arrangements for the pricing of eculizumab and the structured program should be provided to the PBAC for review.

The PBAC considered that a Managed Entry Scheme[[9]](#endnote-9) for eculizumab in aHUS would address the uncertainties around both the incremental effectiveness and cost-effectiveness of eculizumab compared to supportive care.

## Stakeholder consultation on restrictions and managed entry

Following the March 2014 PBAC meeting, the Department negotiated with Alexion regarding the elements of the managed entry scheme recommended by the PBAC and the PBS restrictions, including the initiation and continuation criteria.

The proposed PBS restrictions for eculizumab were developed in an iterative fashion following consultation with clinicians, patients, patient advocates and the sponsor. The consultation process included a stakeholder meeting.

The PBAC considered the available data continued to be of low quality, even when taking into account the difficulties of data collection in rare diseases. However, the PBAC noted that new data regarding aHUS and its management are emerging rapidly, and encouraged the sponsor to submit new data for PBAC consideration as it becomes available, in order to enable further consideration based on more robust evidence. For example, the PBAC noted that evolving fields include: the understanding of aHUS and how treatment should be tailored based on a patient’s genetic sub-type; and the role for monitoring complement activation in an approved assay that can be used in routine clinical practice.

By extending the current subsidy for an additional year, enhancing the information requirement at the 12 month assessment checkpoint (information on factors associated with an increased risk of recurrence and the likely clinical consequence of a recurrence; including 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), stakeholder meetings to clarify the proposed clinical place of this therapy, and adding requirements for additional data reporting at 18 and 24 months, the PBAC will have more comprehensive evidence to review the effectiveness and cost-effectiveness of this medicine in real clinical practice in Australia.

## Reference Group review

In late 2015, the government established an eculizumab expert reference group with experts from the Haematology Society of Australia and New Zealand (HSANZ), the Australian and New Zealand Paediatric Nephrology Association (ANZPNA), and the independent Pharmaceutical Benefits Advisory Committee (PBAC).[[10]](#endnote-10) Its role is to support DHS with administration of requests for continuing treatment by providing an additional level of clinical support. This was to address any concerns about the eligibility of patients for subsidised eculizumab and to ensure no patient is delayed necessary treatment due to Government processes.

In March 2016, the Reference Group reviewed de-identified original applications for patients who commenced PBS-subsidised eculizumab during the first 12 months of listing. Each was considered in terms of whether the information provided by the prescriber satisfied the PBS restriction and whether the clinical data robustly supported a diagnosis of aHUS. The reference group considered that less than half of the patients who commenced eculizumab in the first year of listing had an unequivocal diagnosis of aHUS. The reference group also noted that the proportion of paediatric patients was lower than estimated.

## Areas of uncertainty

Areas of uncertainty in the financial estimates identified by the PBAC and not addressed in submissions to the PBAC included:

* The estimates were highly sensitive to any small change in patient numbers due to the high acquisition cost of eculizumab.
* Lack of reliable data on incidence and prevalence in Australia given the rarity of the condition and inconsistent use of diagnostic criteria in the past.
* Whether all patients would need routine life-long therapy and the optimal duration of therapy.

### Approach taken to estimate utilisation

The submission presented an epidemiological approach to estimate utilisation of eculizumab for aHUS. The approach was based on published literature and a clinician survey.

The submission acknowledged that aHUS is an ultra-rare disease for which prevalence and incidence data are extremely limited. Prevalence of aHUS was estimated to be seven per million[[11]](#endnote-11) from European registry data of a paediatric population. The sponsor assumed that the prevalence rate of aHUS is equal in children and adults.

The PBAC Minutes (March 2013) noted the incidence of aHUS which is approximately 1‑2/100,000 in the general population and 6/100,000 in children. 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.

A diagnosis rate and an eculizumab treatment rate were applied to the prevalence estimate, based on reports from physicians to the sponsor on the number of aHUS patients and their treatment status. The submission evaluation commentary, prepared for the PBAC, considered that “The basis for the assumptions made (e.g. diagnosis rate and uptake rate) is not clear. Therefore, there is a potential for the number of eligible patients to be greater or lower than the estimate in the re-submission.”

The submission considered by PBAC in July 2014 assumed 10 patients would be grandfathered to PBS-listed eculizumab in the first year of listing.

The same submission assumed that, due to the life threatening nature of aHUS, patients are unlikely to discontinue. As such, a discontinuation rate of 5% in Year Two, increasing slightly to 10% in Years Three to Five was assumed based on previous experience with patients suffering from ultra-rare diseases.

The average number of vials per year was calculated based on the proportions of patient weights. The weight distribution was based on aHUS patient data collected locally by the sponsor.

Treatment is recommended at 14 day intervals but may be given more frequently at 12 day intervals if required.No allowance was made for this in the estimates.

### Previous reviews by the DUSC

Eculizumab has not previously been reviewed by the DUSC.

#### Methods

The analyses used data from the Department of Human Services (DHS) supplied prescriptions database for dates of supply up to and including 31 May 2017; extracted 11 August 2017. 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:

* Count of new and continuing patients supplied PBS eculizumab by quarter (Figure 1)
* New and continuing patient counts by year (Table 2)
* Patient age at initiation (Table 3)
* Hospital setting (public or private) based on the pharmacy dispensing eculizumab
* Prescriber type (Figure 2)
* Length of treatment (Figure 3)
* A predicted versus actual utilisation analysis (Table 5)
* Patient weight (Table 7 and Table 8)

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 was 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 e.g. to count grandfathered patients.

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 x median time to resupply (i.e. 3 x 28 days) between supplies, which is an estimated break in treatment of at least 2 x 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 May 2017) if their last prescription was within 3 x 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 the total number of supplies of eculizumab in the same period compared with publicly available Department of Human Services (DHS) Medicare date of processing data.[[12]](#endnote-12)

#### Results

### Analysis of drug utilisation

## Overall utilisation

Figure 1 shows the total number of patients who were supplied eculizumab in each quarter and of those patients how many received their first ever PBS supply of eculizumab in that quarter. 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 the 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 and Appendix B for further restriction details).

The number of patients supplied eculizumab has steadily increased since the time of listing, from 28 in the first month of listing (December 2014) to 72 in the first quarter of 2017 (Figure 1). Of the 28 patients who commenced PBS supply in the first month of listing (December 2014), 22 (79%) were supplied via the grandfathering arrangements (data not shown). A total of 26 patients received eculizumab via the grandfather restriction. After the first quarter, the number of patients new to PBS supply varied within a range of 7 to 18 patients per quarter. A total of 145 unique patients have been supplied eculizumab from the time of PBS listing (1 December 2014) to the most recent data (31 May 2017).

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

Data are presented by quarter of supply. Initiators are total number of people supplied their first PBS-subsidised prescription; this is a subset of PBS patients.

Source: PIN count, DHS supplied prescriptions database to 31 May 2017; extracted 11 August 2017.

Table 2: Patients supplied eculizumab for the treatment of aHUS by year

|  |  |  |
| --- | --- | --- |
| **Year** | **PBS patients** | **PBS initiators** |
| 2014 (Dec only) | 28 | 28 |
| 2015 | 74 | 48 |
| 2016 | 92 | 48 |
| 2017 (Jan-May) | 78 | 21 |

Source: DHS supplied prescriptions database to 31 May 2017; extracted 11 August 2017. Initiators are total number of people supplied their first PBS-subsidised prescription in that year; this is a subset of PBS patients.

The total number of patients and number of new patients by calendar year is shown in Table 2. In 2016, 92 patients were supplied eculizumab under the aHUS restrictions. Of these patients, 48 (52%) received their first PBS-subsidised supply of eculizumab.

## Utilisation by age

The submission defined paediatric aHUS patients as less than 12 years of age. Table 3 shows that, from the time of listing to the most recent data, the proportion of adult patients (12 years and over) was 93%. Data is 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.

Table 3: Patient age at initiation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Child**  **(0-11 years)** | **Adult**  **(12+ years)** | **Total PBS initiators** | **% adult** |
| **Total Patients** | 10 | 135 | 145 | 93% |

Time period: December 2014 – May 2017.

Source: DHS supplied prescriptions database to 31 May 2017; extracted 11 August 2017.

## 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 (May 2017). The difference in cost between the public and private hospital prescriptions ($47.15) is small as a proportion of total cost per supply.

## Utilisation by prescriber type

Figure 2 presents prescriptions by prescriber type in the second year of PBS listing (December 2015 to November 2016). In this period, the specialty that prescribed the highest number of supplied prescriptions was nephrologists (317 prescriptions; 45% of prescriptions supplied). This was followed by non-vocationally registered general practitioners (143 prescriptions; 20%) and haematologists (93 prescriptions; 13%). The majority of supplied prescriptions were written by specialists. 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. non-vocationally registered general practitioners) to prescribe eculizumab in consultation with the primary specialist managing the patient care.

**Figure 2: Prescriptions supplied in Year 2 of eculizumab listing by prescriber type**

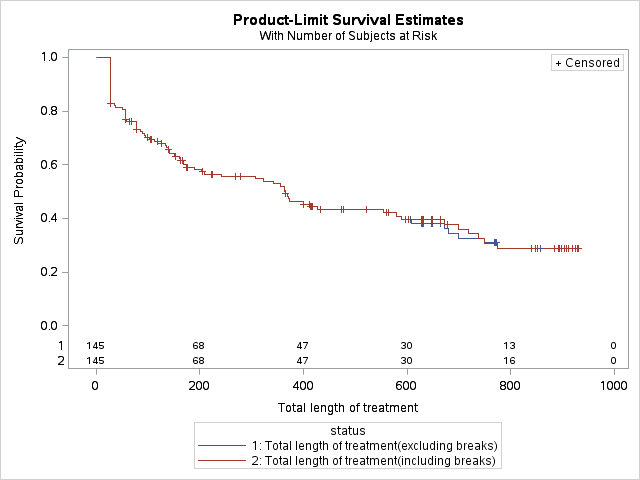
Year 2 = December 2015 – November 2016. NONVRGP = non-vocationally registered general practitioner

Source: DHS supplied prescriptions database to 31 May 2017; extracted 11 August 2017.

## Duration of therapy

Figure 3 depicts the length of treatment analysis. The total period of observation of prescriptions supplied was 1 December 2014 to 31 May 2017. Prescriptions supplied for all 145 patients were included.

Under the definition that allows for right censoring 63 patients were deemed to be continuing treatment at the end of the data period (i.e. end of May 2017). The mean duration of therapy was 403 days excluding breaks and 405 days including breaks. Accounting for the time patients have breaks in therapy (no supply of eculizumab for more than 3x28 days) made no difference to the median duration of therapy (365 days). This implies that very few patients have a substantial break from treatment. In Figure 3 the lines diverge around 600 days on treatment. This implies that only patients who have received over 600 days of treatment with eculizumab on the PBS have breaks in supply. It is not possible to obtain the reason for any discontinuation of supply from the available data.



**Figure 3: Length of treatment analysis using the Product-Limit method**

Source: DHS supplied prescriptions database to 31 May 2017; extracted 11 August 2017.

### Analysis of expenditure

$71.5 million in PBS benefits have been paid for eculizumab since its listing in December 2014 (Table 4).

Table 4: Government cost (Benefits paid) for eculizumab for the treatment of aHUS

|  |  |
| --- | --- |
| **Year** | **PBS benefits** |
| Year 1 (Dec ’14 – Nov ’15) | $21,937,626 |
| Year 2 (Dec ’15 – Nov ’16) | $32,088,003 |
| Year 3 (Dec ’16 – May ’17; i.e. 6 months) | $17,453,390 |
| **Total** | **$71,479,019** |

Source: DHS supplied prescriptions database to 31 May 2017; extracted 11 August 2017.

As this analysis was based on date of supply, there may be small differences between these results and publicly available Medicare Australia date of processing data.

### Analysis of actual versus predicted utilisation

Use of eculizumab for aHUS in terms of the number of patients, vials and expenditure was more than double what was predicted in both the first and second years of listing (Table 5).

Table 5: Predicted versus actual use of eculizumab for aHUS

|  | **Year 1**  **Dec ’14 – Nov ‘15** | **Year 2**  **Dec ’15 – Nov ‘16** |
| --- | --- | --- |
| **Patients** | | |
| Predicted | ''''' | ''''' |
| Actual | 69 | 93 |
| % Difference (A-P)/P | ''' ''''''''''' | ''' ''''''''''' |
| **Vials** | | |
| Predicted | ''''''''''' | '''''''''' |
| Actual | 3,691 | 5,399 |
| % Difference (A-P)/P | '' '''''''''' | ''' '''''''''''' |
| **Expenditure** | | |
| Predicted | '''''''''''''''''''''''' | ''''''''''''''''''''''' |
| Actual | $21,937,626 | $32,088,003 |
| % Difference (A-P)/P | ''' '''''''''' | ''' '''''''''''' |

Source: predicted values from final estimates agreed between the Sponsor and the Department prior to listing. Actual values from DHS supplied prescriptions database to 31 May 2017; extracted 11 August 2017.

Table 6: Predicted versus actual number and proportion of patients by age

|  |  |  |
| --- | --- | --- |
|  | **Predicted** | **Actual** |
| Adult patients (12+ years) | ''''' '''''''''''' | 109 (92%) |
| Paediatric patients (0-11 years) | ''''' ''''''''''' | 9 (8%) |

Actual data for the first two years of listing (December 2014 – November 2016); actual initiators: n= 118. Actual age at initiation i.e. at the time of the first prescription supplied.

Source: DHS supplied prescriptions database to 31 May 2017; extracted 11 August 2017.

The estimates assumed that approximately ''''''''''''''''''''' of patients would be treated with the adult dose (body weight ≥ 40 kg). Actual data shows that 92% of initiating patients in the first two years of listing were aged 12 years and over at the time of their first prescription (Table 6). This is consistent with the weight data reported through the written authority applications to DHS (Table 7), which shows 91% of patients with a recorded weight of 40 kg or more (n=122; see Table 8 for descriptive statistics of the sample). There is a slight difference in initiating patient numbers between the DHS authority approvals (n = 128) and DHS supplied prescriptions database (n = 118); as there may be a time lag between an authority being granted and supplied, or the authority might not have been supplied.

Table 7: Proportion of patients over and under 40 kg

|  |  |  |
| --- | --- | --- |
| **Mass range** | **Number of patients** | **Percentage of patients** |
| < 40 kg | 11 | 9% |
| ≥ 40 kg | 111 | 91% |

Data for the first two years of listing (December 2014 – November 2016); mass at first authority application. Six patients had no mass recorded.

Source: DHS Authority Approvals

Table 8: Descriptive statistics for patient mass

|  |  |
| --- | --- |
| Count | 122 |
| Mean | 67 |
| Median | 69 |
| Mode | 80 |
| Max | 134 |
| Min | 11 |
| Standard deviation | 21 |

Data for the first two years of listing (December 2014 – November 2016); mass at first authority application. Six patients had no mass recorded.

Source: DHS Authority Approvals

#### Discussion

Possible reasons for higher than expected use of eculizumab includes:

* **Prevalence and incidence data were uncertain**. Prevalence of aHUS was estimated to be seven per million11 from European registry data of a paediatric population. The submission used this prevalence rate to estimate the number of patients with aHUS, but then applied a diagnosis rate and a treatment rate; this method may have underestimated the number of treated patients. Additionally, the submission assumed that the prevalence rate in children could be applied to adults, which may not have been reasonable.
* **Use to treat TMA due to causes other than aHUS**; noting that the Eculizumab Expert Reference Group was instated to provide an additional level of clinical support to ensure the correct decisions are made regarding an individual patient’s circumstances for applications seeking continuation and re-initiation of treatment beyond 1 December 2015.10
* **Fewer discontinuations than expected**. The submission assumed 5% of patients would discontinue in Year 2. Research into the appropriate duration of treatment with eculizumab and the risks of prolonged therapy is ongoing.7,[[13]](#endnote-13) Eculizumab treatment is often maintained to prevent relapses and reactivation of the renal TMA process.7,[[14]](#endnote-14) However, it has been suggested that the risk of treatment-related adverse events and the high cost of the therapy necessitate further studies to investigate treatment withdrawal and alternative therapeutic options.7 Some studies suggest that the presence and nature of genetic mutations may affect the capacity to successfully withdraw eculizumab treatment; discontinuation of eculizumab in patients without rare complement gene variants may be safer.14,[[15]](#endnote-15) The Global aHUS Registry, the largest aHUS registry by number of enrolled patients, recently assessed eculizumab treatment, discontinuation and reinitiation. Data from the registry show that among 406 patients enrolled from 13 countries, 235 (57.9%) patients received eculizumab for a mean duration of 0.4 years, 46 (20%) patients discontinued eculizumab and 5 (10%) restarted the drug.14 These duration and discontinuation patterns differ from what was observed in the Australian PBS data.

These reasons relate to uncertainties that were previously identified by the PBAC (see Areas of uncertainty). The PBAC sought to address these uncertainties and contain risks in its recommendations that:

* access to the listing be by written authority application;
* the sponsor rebate the Commonwealth 100% of spending over the financial estimates in the submission;
* the sponsor rebate the Commonwealth the price of eculizumab provided to patients who do not achieve a complete remission to treatment;
* a Managed Entry Scheme for eculizumab in aHUS be implemented to address the uncertainties around both the incremental effectiveness and cost-effectiveness of eculizumab compared to supportive care (see Recommendation section).

Discrepancy in the degree to which the patients and vials are higher than expected could be influenced by a different proportion of paediatric to adult doses than expected, or a different proportion of new, maintenance and discontinuing patients than expected. The results of the analysis do not suggest a more frequent treatment schedule, as the median time to resupply is 28 days. However, varying supply arrangements for IV infusions may mean that the date of supply of the drug does not correlate with the date of infusion.

#### Conclusion

Use of eculizumab for aHUS in terms of the number of patients, vials and expenditure was more than double what was predicted in both the first and second years of listing.

DUSC and the PBAC may wish to consider whether to review eculizumab utilisation in a further 12 months’ time. From the current data it is not possible to tell whether the patient numbers are starting to plateau or will continue to rise. Principal issues for further investigation may be the number of treated patients and the extent to which patients continue treatment. This may also provide an opportunity to analyse additional data that became available as a result of the restriction changes in February 2016; e.g. recording of factors associated with an increased risk of recurrence and the likely clinical consequence of a recurrence; including 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.

#### DUSC consideration

DUSC noted that the main areas of uncertainty in the eculizumab financial estimates were the lack of reliable Australian epidemiological data for aHUS and the optimal duration of therapy. The estimates were highly sensitive to any small change in patient numbers due to the high acquisition cost of eculizumab. DUSC noted that eculizumab use has been significantly higher than predicted. DUSC considered that a number of factors may have driven this difference.

Prevalence of aHUS in the submission was estimated to be seven per million from European registry data of a paediatric population. The sponsor response supported the PBAC view that the lack of reliable epidemiological data for aHUS was an area of uncertainty that may have contributed to inaccurate projections of use, noting limitations in sourcing reliable epidemiological data in ultra-rare diseases. The sponsor response also noted that, while there are no published data on the impact of eculizumab on prevalence and incidence of aHUS, a combination of increased awareness of the disease in the medical community and improved survival could explain the higher than projected use of eculizumab. DUSC agreed that uncertain estimates of Australian aHUS prevalence at the time of listing may be one factor contributing to the higher than expected use of eculizumab. DUSC also noted there were more grandfathered patients than predicted. The sponsor considered this was due to the 19 additional aHUS patients provided eculizumab during the intervening period between submission and PBS listing who were subsequently grandfathered to PBS-subsidised treatment.

The submission used this prevalence rate to estimate the number of patients with aHUS, but then applied a diagnosis rate and a treatment rate. DUSC agreed with the report that this method may have underestimated the number of treated patients.

The report suggested discrepancy in the degree to which the patients and vials are higher than expected could be influenced by a different proportion of paediatric to adult doses than expected, or a different proportion of new, maintenance and discontinuing patients than expected. The submission assumed that the prevalence rate in children could be applied to adults, which may not have been reasonable. The sponsor reiterated that the aforementioned challenge in predicting aHUS incidence and prevalence also pertains to accurately estimating the split between adult and paediatric patients. The results of the analysis do not suggest a more frequent treatment schedule, as the median time to resupply is 28 days. However, varying supply arrangements for IV infusions may mean that the date of supply of the drug does not correlate with the date of infusion. DUSC noted these areas of uncertainty.

There were fewer discontinuations than expected. The submission assumed 5% of patients would discontinue in Year 2. Research into the appropriate duration of treatment with eculizumab and the risks of prolonged therapy is ongoing. The sponsor responded that, consistent with the TGA approved label, Australian treatment practice demonstrates that the only reason for discontinuation should be when clinically indicated. The sponsor presented additional references that demonstrate the need for ongoing eculizumab treatment in patients with aHUS to avoid further thrombotic microangiopathy (TMA) manifestations. The sponsor noted that the timing of TMA in patients who discontinue therapy is unpredictable and the consequences of subsequent TMA can be unpredictable and severe. DUSC questioned why any patients would be discontinued in the absence of supportive clinical data. DUSC considered that patients who stopped after 600 days would not be stopping due to intolerance. DUSC questioned whether these patients might be going on to transplant.

The report noted that possible use of eculizumab to treat TMA due to causes other than aHUS may have contributed to higher than expected eculizumab use; noting the creation of the Eculizumab Expert Reference Group and changes to the eculizumab restrictions to support clinical decisions. The sponsor supported the introduction of revised restriction criteria, including the requirement for clinician cover letters, in the eculizumab application process. The sponsor considered this documented rationale and exclusion of alternative causes of TMA has addressed any risk of eculizumab use outside the restriction. DUSC recalled the changes that have been made to the restriction criteria, including administrative arrangements, with increasing understanding of Australian clinical practice in using eculizumab for the treatment of aHUS. DUSC acknowledged the important role of expert clinicians in clarifying the clinical place for eculizumab in aHUS.

These reasons relate to uncertainties that were previously identified by the PBAC. The PBAC sought to address these uncertainties and contain risks in its recommendations that:

* access to the listing be by written authority application;
* the sponsor rebate the Commonwealth 100% of spending over the financial estimates in the submission;
* the sponsor rebate the Commonwealth the price of eculizumab provided to patients who do not achieve a complete remission to treatment;
* a Managed Entry Scheme for eculizumab in aHUS be implemented to address the uncertainties around both the incremental effectiveness and cost-effectiveness of eculizumab compared to supportive care (see Recommendation section).

DUSC considered that if a Risk Sharing Arrangement (RSA) had been in place it would have helped manage the risks noted by PBAC originally and contained the cost to government. The sponsor response stated that as a result of the changes that have been made to the listing over time, and in acknowledgement of the need to budget certainty for government forward estimates, Alexion is committed to working with the Department to negotiate a RSA for the aHUS listing.

DUSC noted that from the current data it is not possible to tell whether the patient numbers are starting to plateau or will continue to rise. Principal issues for further investigation may be the number of treated patients and the extent to which patients continue treatment. This may also provide an opportunity to analyse additional data that became available as a result of the restriction changes in February 2016; e.g. recording of factors associated with an increased risk of recurrence and the likely clinical consequence of a recurrence; including 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.

#### DUSC Actions

* Given use beyond predictions and the high cost of the medicine, DUSC requested a further review of eculizumab use in 12 months’ time.
* DUSC requested that the report be provided to the PBAC and the Eculizumab Expert Reference Group.

#### 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 as acknowledged in this DUSC review and as a result of the changes that have been made to the listing over time, and in acknowledgement of the need to budget certainty for government forward estimates, is committed to working with the Department of Health to negotiate a RSA for the aHUS listing of eculizumab going forward.

#### 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.

To the fullest extent permitted by law, neither the DoH nor any DoH employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person’s use or misuse of the information available from this report or contained on any third party website referred to in this report.

#### References

#### Appendix A

Table A1: abridged eculizumab restrictions (August 2017)

| **x** | |
| --- | --- |
| **Condition:** aHUS | |
| **Treatment phase:** Initial treatment | |
| **Clinical criteria** | * 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 30x10^9/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.   The restriction provides definitions for evidence of active and progressing TMA. |
| **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** | * 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** | * 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.   The restriction provides definitions of treatment response. |
| **Treatment Phase:** Continuing treatment | |
| **Clinical criteria** | * 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.   The restriction provides definitions of treatment response. |
| **Treatment Phase:** ExtendedContinuing treatment | |
| **Clinical criteria** | * 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.   The restriction provides definitions of treatment response. |
| **Treatment Phase:** Recommencement of treatment | |
| **Clinical criteria** | * 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 10^9/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.   The restriction provides definitions of treatment response. |
| **Treatment Phase:** Continuing recommencement of treatment | |
| **Clinical criteria** | * 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.   The restriction provides definitions of treatment response. |

Source: PBS website. Current at August 2017.

#### Appendix B

Table B1: changes to eculizumab restrictions

| **Date** | **Changes to restriction** |
| --- | --- |
| **Initial** | |
| 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 | Added clarification that:   * the active and progressing TMA must be caused by aHUS. * 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.   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.’  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.’  Added that the written authority application:   * must include ‘a detailed cover letter from the prescriber.’ * 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. |
| **Initial – balance of supply** | |
| 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. |
| **Extended Initial (listed November 2015)** | |
| November 2015 | Restrictions for ‘Continuing treatment - New patient’ and ‘Continuing treatment - following recommencement of treatment after an initial 52-week period’ introduced. |
| February 2016 | The two restrictions above were changed to ‘Extended initial treatment – Assessment phase.’  Removed specification of the number of weeks’ therapy that the patient must have received under the initial restriction.  ‘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.’  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).’  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…’  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.’ |
| January 2017 | Added that the written authority application:   * must include ‘a detailed cover letter from the prescriber.’ * 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. |
| **Continuing (listed December 2014)** | |
| February 2016 | Removed ‘new patient’ from continuing treatment  Removed specification of the number of weeks’ therapy that the patient must have received under the initial restriction.  Removed ‘per continuing treatment course authorised’ from the maximum weeks of treatment.  Added ‘The authority application must include the following measures of response to the prior course of treatment…’  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…’  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.’ |
| January 2017 | Added that the written authority application:   * must include ‘a detailed cover letter from the prescriber.’ * 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. |
| **Extended continuing (listed December 2014)** | |
| November 2015 | Changed from ‘continuing treatment beyond initial 48 weeks of treatment’ to ‘continuing treatment beyond initial 52 weeks of treatment.’ |
| February 2016 | Changed from ‘continuing treatment beyond initial 52 weeks of treatment’ to ‘Extended Continuing treatment.’  Added ‘per continuing treatment course authorised’ to the maximum weeks of treatment.  Added ‘The authority application must include the following measures of response to the prior course of treatment…’  Rewording around timing requirements for haematological results.  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…’  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.’ |
| January 2017 | Added that the left-ventricular ejection fraction and TMA-related pulmonary impairment must be based on current objective measurement  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.  Added that the written authority application:   * must include ‘a detailed cover letter from the prescriber.’ * 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. |
| **Recommencement** | |
| November 2015 | Changed from recommencement after 48 weeks to recommencement after 52 weeks |
| February 2016 | Changed from ‘Initial 2 – recommencement’ to ‘Recommencement’  Removed the time requirement (52 weeks) from the length of previous treatment.  Added ‘The authority application must include the following measures of response to the prior course of treatment…’  Rewording around timing requirements for haematological results.  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…’  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.’ |
| January 2017 | Added that the written authority application:   * must include ‘a detailed cover letter from the prescriber.’ * 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. |
| **Continuing recommencement (listed December 2014)** | |
| February 2016 | Changed references to previous treatment under ‘Initial 2 – recommencement’ to ‘Recommencement’  Removed the time requirement (48 weeks) from the length of previous treatment.  Added ‘The authority application must include the following measures of response to the prior course of treatment…’  Rewording around timing requirements for haematological results.  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…’  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.’ |
| January 2017 | Added that the written authority application:   * must include ‘a detailed cover letter from the prescriber.’ * 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. |
| **Grandfathered** | |
| February 2016 | Changed from ‘Initial 3 – grandfathered’ to ‘Grandfather’  Changed references from ‘Continuing treatment New Patient’ to ‘Extended Initial.’  ‘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).’  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…’  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.’ |
| January 2017 | Grandfather restriction ceased. |

1. Soliris® (eculizumab, *rmc*). Australian Approved Product Information. Frenchs Forest: Alexion Pharmaceuticals Australasia Pty Ltd. Approved 20 March 2009, updated 22 June 2016. Available from <<https://www.tga.gov.au/product-information-pi>> [↑](#endnote-ref-1)
2. NICE Eculizumab for treating atypical haemolytic uraemic syndrome, Information for the public, published 28 January 2015. Available from <<https://www.nice.org.uk/guidance/hst1/resources/eculizumab-for-treating-atypical-haemolytic-uraemic-syndrome-2541213637>> [↑](#endnote-ref-2)
3. Soliris® (eculizumab, *rmc*). Consumer Medicine Information. Frenchs Forest: Alexion Pharmaceuticals Australasia Pty Ltd. Updated June 2016. Available from <<https://www.tga.gov.au/consumer-medicines-information-cmi>> [↑](#endnote-ref-3)
4. Campistol JM, Arias M, Ariceta G, Blasco M, Espinosa L, Espinosa M, et al. Actualización en síndrome hemolítico urémico atípico: diagnóstico y tratamiento. Documento de consenso. Nefrologia 2015; 35: 421–447. doi:10.1016/j.nefroe.2015.11.006 [↑](#endnote-ref-4)
5. The Pharmaceutical Benefits Advisory Committee Public Summary Document for eculizumab March 2014. Available at <<http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-03/eculizumab-psd-03-2014>> [↑](#endnote-ref-5)
6. Kaplan BS, Ruebner RL, Spinale JM, Copelovitch L. Current treatment of atypical haemolytic uremic syndrome. Intractable & Rare Diseases Research 2014; 3(2): 34-45. doi:10.5582/irdr.2014.01001. [↑](#endnote-ref-6)
7. Quiroga B, de Lorenzo A, Vega C, de Alvaro F. A Case Report and Literature Review of Eculizumab Withdrawal in Atypical Hemolytic Uremic Syndrome. American Journal of Case Reports 2016; 17: 950-956. doi:10.12659/AJCR.899764. [↑](#endnote-ref-7)
8. Department of Health. Positive recommendations made by the PBAC July 2017. Canberra, Australia. Available from <<http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-pbac-july-2017>>. [↑](#endnote-ref-8)
9. Department of Health. Framework for the introduction of a Managed Entry Scheme for submissions to the Pharmaceutical Benefits Advisory Committee. Canberra, Australia. Available from <<http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-PBAC-submissions>> [↑](#endnote-ref-9)
10. Department of Health. Eculizumab – Expert Reference Group and application process for patients and clinicians. Canberra, Australia. Available from <<http://www.pbs.gov.au/info/general/eculizumab-expert-reference-group>>. [↑](#endnote-ref-10)
11. Taylor CM, Machin S, Wigmore SJ, Goodship THJ. Clinical Practice Guidelines for the management of atypical Haemolytic Uraemic Syndrome in the United Kingdom. British Journal of Haematology 2009; 148: 37‑47. doi:10.1111/j.1365-2141.2009.07916.x [↑](#endnote-ref-11)
12. PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>. [↑](#endnote-ref-12)
13. Zhang K, Lu, Y, Harley KY, Tran MH. Atypical Hemolytic Uremic Syndrome: A Brief Review. Hematology Reports 2017; 9(2): 7053. doi:10.4081/hr.2017.7053. [↑](#endnote-ref-13)
14. Rodriguez E, Barrios C, Soler MJ. Should eculizumab be discontinued in patients with atypical hemolytic uremic syndrome? Clinical Kidney Journal 2017; 10(3): 320–322. doi:10.1093/ckj/sfx024. [↑](#endnote-ref-14)
15. Sahutoglu T, Basturk T, Sakaci T, Koc Y, Ahbap E, Sevinc M, et al. Can eculizumab be discontinued in aHUS?

    Case report and review of the literature. Medicine 2016; 95(31): e4330. doi:10.1097/MD.0000000000004330. [↑](#endnote-ref-15)