Technology Guidance

Complement inhibitors

for treating paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Eculizumab 300 mg concentrate for solution for infusion as monotherapy for paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS) in adults and children.

Funding status

Eculizumab 300 mg concentrate for solution for infusion is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indications from 1 April 2026.

Eculizumab should be used in line with the additional clinical criteria listed in the Annex.

MAF assistance **does not** apply to iptacopan or ravulizumab for treating PNH or aHUS.

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Technology evaluation

1.1. At the November 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of complement inhibitors for first-line treatment of paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS).

1.2. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical and patient experts from public healthcare institutions. Published clinical and economic evidence for the complement inhibitors was considered in line with their registered indications. Three complement inhibitors – eculizumab, iptacopan, and ravulizumab – were evaluated for PNH. In addition, eculizumab and ravulizumab were evaluated for aHUS.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. The Committee noted that both PNH and aHUS are blood disorders characterised by dysregulation of the complement system (a part of the body's immune system). Clinical practice guidelines have recommended complement inhibitors for first-line treatment of PNH and aHUS. Eculizumab and ravulizumab are complement C5 inhibitors that work by blocking terminal complement activation, whereas iptacopan is a factor B inhibitor that targets the alternative complement pathway (upstream of C5). The Committee noted that best supportive care (BSC) remains tailored to individual patient needs. For PNH, BSC may include blood transfusions, anticoagulants, and nutritional supplements. For aHUS, BSC may include dialysis, plasma exchange, and plasma infusion.

2.2. PNH arises from an acquired mutation of the phosphatidylinositol glycan A (PIG-A) gene within bone marrow stem cells. The mutation results in a lack of complement-inhibiting proteins in red blood cells and leads to uncontrolled activation of the complement system. This causes intravascular haemolysis, anaemia, increased thrombosis risk, and potentially organ damage and other serious, systemic complications. The Committee noted that, despite BSC, PNH was associated with mortality rates of approximately 35% at 5 years and 50% at 10 years.

2.3. PNH can occur at any age but is most often diagnosed in young adults in their 30s or 40s. The global incidence is estimated at 1–1.5 cases per million people. In Singapore, epidemiological data for PNH remains limited, although at least 10 patients with the condition are currently estimated to require treatment with complement inhibitors.

2.4. The second condition, aHUS, is a life-threatening blood disorder. It may result from inherited or acquired dysregulation of complement system proteins, which triggers uncontrolled complement activation. This causes severe inflammation of blood vessels and the formation of blood clots in small blood vessels throughout the body, a process known as thrombotic microangiopathy. The clinical manifestations include haemolytic anaemia, thrombocytopaenia and ischaemic organ damage, especially in the kidneys.

2.5. The prognosis for untreated aHUS is poor. Approximately 10–15% of patients may die during the acute phase of the disease. Within a year of diagnosis, up to 70% of patients may progress to end-stage kidney disease requiring dialysis or die. The use of BSC also had limited impact on disease morbidity and mortality.

2.6. aHUS can occur in both children and adults. The global incidence is estimated to range from 0.23 to 1.9 cases per million people. In Singapore, there is limited epidemiological data for aHUS, although at least 4 patients with the condition are currently estimated to require treatment with complement inhibitors.

2.7. The Committee considered 10 testimonials from local patients and carers about their lived experiences with PNH and noted that no patients with aHUS provided inputs. The Committee acknowledged that PNH had a profound physical, emotional and social impact on patients' daily lives. Fatigue, weakness, reduced immunity, shortness of breath and complications affected their ability to work, play sports, perform daily activities and socialise. Patients were receiving various treatments for PNH, including blood transfusions, blood thinners and complement inhibitors. The financial burden of treatments, tests, scans and hospitalisations was the patients' greatest concern. Overall, patients considered that any new treatment for PNH should lower the risk of serious complications, be more affordable and accessible, extend survival, allow them to carry out daily activities independently, and reduce the need for blood transfusions.

2.8. Overall, the Committee acknowledged that there was a high clinical need to consider complement inhibitors for funding, to ensure appropriate patient care and improve treatment affordability.

Clinical effectiveness and safety

3.1. PNH

The Committee reviewed the clinical evidence for eculizumab, ravulizumab, and iptacopan as monotherapy for first-line treatment of PNH in patients who presented with haemolysis. In line with their respective regulatory approvals, eculizumab and ravulizumab were assessed for use in both adult and paediatric populations, whilst iptacopan was assessed in adult patients only.

3.2. For eculizumab, four key clinical trials were identified: a randomised placebo-controlled trial (TRIUMPH) and two single-arm long-term studies (SHEPHERD and E05-001) conducted in adults, as well as a single-arm study (M07-005) conducted in children.

3.3. Results of the 26-week TRIUMPH trial showed that eculizumab was more efficacious than placebo in reducing haemolysis, stabilising haemoglobin levels, reducing the need for blood transfusions and improving health-related quality of life. In long-term studies (with total eculizumab exposure time of up to 54 months), eculizumab's treatment effects were sustained, with fewer thrombotic events reported during treatment compared to the pre-treatment period. In the 12-week single-arm paediatric study (M07-005), the efficacy of eculizumab was generally consistent with that observed in adults.

3.4. For ravulizumab, three key trials were identified: two randomised controlled trials (Studies 301 and 302) that compared ravulizumab with eculizumab in adults who were either naïve to complement inhibitor treatment or clinically stable on eculizumab, and a single-arm trial (Study 304) conducted in children.

3.5. Results of Studies 301 and 302 showed that ravulizumab was non-inferior to eculizumab in outcomes such as transfusion avoidance and lactate dehydrogenase normalisation (indicating a reduction in haemolysis) at 26 weeks. Hence, treatment with ravulizumab provided similar clinical benefit as eculizumab in adults with PNH. In children, the efficacy of ravulizumab was generally consistent with that observed in adults.

3.6. For iptacopan, a single-arm study (APPOINT-PNH) in adults was identified. The results at 24 weeks showed that iptacopan treatment led to an increase in haemoglobin levels, and reductions in fatigue and the need for blood transfusions, compared to baseline values. In the absence of head-to-head trials between iptacopan and either eculizumab or ravulizumab, the Committee considered the results of indirect treatment comparisons (ITCs) that had been reviewed by NICE (UK). While the ITCs suggested that iptacopan was more effective than eculizumab or ravulizumab, NICE considered these results uncertain due to the limitations of unanchored indirect comparisons.

3.7. In terms of safety, the three complement inhibitors were generally well-tolerated in their clinical trials, with low rates of adverse events (AEs) leading to treatment discontinuation. The treatment-emergent AEs commonly reported with these complement inhibitors included headache and upper respiratory tract infection.

3.8. Overall, based on the available evidence, the Committee considered eculizumab and ravulizumab to be likely comparable in terms of effectiveness and safety for the treatment of PNH. However, the clinical comparability of iptacopan with eculizumab or ravulizumab remained uncertain.

3.9. aHUS

The Committee reviewed the clinical evidence for eculizumab and ravulizumab as monotherapy for first-line treatment of aHUS in adults and children with active disease.

3.10. A total of five key single-arm studies were identified: three for eculizumab (C08-002, C10-003 and C10-004), and two for ravulizumab (Studies 311 and 312). All five studies comprised a 26-week initial treatment period, followed by an extension phase (up to 3 years for eculizumab and 4.5 years for ravulizumab).

3.11. Results of these studies showed that both eculizumab and ravulizumab were efficacious in reducing haemolysis, normalising platelet count, and improving kidney function and health-related quality of life. Among patients who required dialysis at study entry, the majority (approximately 80%) were able to discontinue dialysis by week 26.

3.12. The safety profiles of eculizumab and ravulizumab were generally manageable, with a low incidence of treatment discontinuation due to AEs across studies.

3.13. In the absence of head-to-head trials between eculizumab and ravulizumab, the Committee considered the results of ITCs that had been reviewed by NICE (UK) and PBAC (Australia). While acknowledging the uncertainty associated with ITCs, the Committee noted that eculizumab and ravulizumab were likely to be comparable in effectiveness and safety.

3.14. Overall, the Committee agreed eculizumab and ravulizumab were effective and safe treatments that were expected to meaningfully improve the prognosis and clinical outcomes of patients with aHUS.

Cost effectiveness

4.1. The Committee reviewed economic evaluations from overseas HTA agencies, which reported high incremental cost-effectiveness ratios (ICERs) when complement inhibitors were compared with BSC in patients with PNH or aHUS. However, the ICERs were noted to be uncertain and difficult to interpret due to various issues, such as limitations with the model structure and concerns that the model did not fully capture the benefits of treatment. To address the evidence uncertainty and improve cost effectiveness of the treatments, the agencies used a combination of approaches. These included price reductions, risk-sharing arrangements and/or clinical criteria for starting and continuing treatment.

4.2. In Singapore, the companies of eculizumab, ravulizumab and iptacopan were invited to submit pricing proposals for their products for funding consideration. The Committee noted that eculizumab had the lowest treatment costs for PNH and aHUS compared to ravulizumab and iptacopan.

4.3. When compared with prices in overseas reference jurisdictions, the Committee considered eculizumab likely to represent an acceptable use of healthcare resources in Singapore for treating PNH and aHUS. The Committee also acknowledged that the company's pricing proposal for eculizumab was adequate to manage the uncertainty of the overall budget impact.

Estimated annual technology cost

5.1. The Committee noted that the cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million in the first year, and between SG$3 million and SG$5 million in the fifth year of listing eculizumab on the MOH List of Subsidised Drugs for treating both PNH and aHUS.

Recommendations

6.1. Given the high clinical need for an effective treatment for PNH and aHUS, the totality of clinical evidence, and that eculizumab is considered an acceptable use of healthcare resources, the Committee recommended eculizumab 300 mg concentrate for solution for infusion be listed on the Medication Assistance Fund (MAF) for treating PNH and aHUS in adults and children.

6.2. The Committee also recommended eculizumab be used in line with additional clinical criteria (listed in the Annex) to govern appropriate use in local practice. The criteria were developed in consultation with local clinical experts and are consistent with overseas reimbursement criteria.

6.3. The Committee recommended not listing iptacopan and ravulizumab on the MOH List of Subsidised Drugs for treating PNH or aHUS due to unfavourable cost effectiveness compared with eculizumab.

ANNEX

MAF clinical criteria for eculizumab for treating paroxysmal nocturnal haemoglobinuria (PNH)

1) **As monotherapy for initial treatment of PNH in adults and children.**
   - Patient must have a diagnosis of PNH established by flow cytometry; and
   - Patient must have a PNH granulocyte clone size ≥10%; and
   - Patient must have a raised lactate dehydrogenase (LDH) value ≥1.5 times the upper limit of normal; and
   - Patient must have **at least one** of the following:
     - Experienced a thrombotic/embolic event which required anticoagulant therapy; or
     - Been transfused with at least 4 units of red blood cells in the last 12 months; or
     - Chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple haemoglobin measurements not exceeding 7 g/dL *in the absence* of anaemia symptoms; or
     - Chronic/recurrent anaemia, where causes other than haemolysis have been excluded, together with multiple haemoglobin measurements not exceeding 10 g/dL *in addition to* having anaemia symptoms; or
     - Debilitating shortness of breath/chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded; or
     - A history of renal insufficiency, demonstrated by an eGFR ≤60 mL/min/1.73m^2, where causes other than PNH have been excluded; or
     - Recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded; or
     - Pregnancy with a high risk of thrombosis or history of gestational complications;

     and
   - Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of PNH.

   For continuation of treatment:
   - Clinical improvement or stabilisation of the condition must have been demonstrated after patient has received eculizumab for at least 6 months. The assessment should include laboratory investigations such as haemoglobin, platelets, white cell count, reticulocytes, neutrophils, granulocyte clone size, and LDH; and
   - Re-assessments must be undertaken at least every 6 months to evaluate whether treatment should be continued.

2) **As monotherapy for PNH in adults and children who are switching from another complement inhibitor to eculizumab.**
   - Patient must have a diagnosis of PNH established by flow cytometry; and
   - Patient requires a switch to eculizumab treatment due to reasons such as, but not limited to, pregnancy, planning pregnancy, or the previous complement inhibitor treatment is not included on the MOH List of Subsidised Drugs; and

- Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of PNH.

For continuation of treatment:

- Clinical improvement or stabilisation of the condition must have been demonstrated after patient has received eculizumab for at least 6 months. The assessment should include laboratory investigations such as haemoglobin, platelets, white cell count, reticulocytes, neutrophils, granulocyte clone size, and LDH; and
- Re-assessments must be undertaken at least every 6 months to evaluate whether treatment should be continued.

MAF clinical criteria for eculizumab for treating atypical haemolytic uraemic syndrome (aHUS)

1) As monotherapy for initial treatment of aHUS in adults and children.

- Patient must have active and progressing thrombotic microangiopathy (TMA) caused by aHUS; and
- Patient must have ADAMTS-13 activity of ≥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 >30x10^9/L, as well as serum creatinine (sCr) >150 µmol/L in adults or sCr greater than the age-appropriate upper limit of normal (ULN) in children; 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 be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of aHUS.

Evidence of active and progressing TMA is defined by the following:

I. (a) Evidence of microangiopathic haemolytic anaemia, as demonstrated by the presence of **at least two** of the following:
    - Presence of schistocytes on blood film;
    - Platelet count <150 x 10^9/L or ≥25% decrease from baseline platelet count;
    - Low or absent haptoglobin;
    - Lactate dehydrogenase (LDH) above normal range;

    OR

    (b) In recipients of a kidney transplant for end-stage kidney disease due to aHUS, a kidney biopsy confirming TMA;

AND

II. Evidence of **at least one** of the following clinical features of active TMA-related organ damage or impairment:
    (a) Kidney impairment as demonstrated by **one or more** of the following:
    - A decline in eGFR of >20% in a patient who has pre-existing kidney impairment;

- A sCr greater than the ULN in a patient who has no history of pre-existing kidney impairment;
- A sCr greater than the age-appropriate ULN in children;
- A renal biopsy consistent with aHUS;

(b) Onset of TMA-related neurological impairment;
(c) Onset of TMA-related cardiac impairment;
(d) Onset of TMA-related gastrointestinal impairment;
(e) Onset of TMA-related pulmonary impairment.

Periodic assessments should be conducted to evaluate whether the patient still requires treatment with eculizumab for aHUS.

For continuation of treatment:

- After patient has received eculizumab for at least 3 - 6 months, patient must have demonstrated on-going treatment response and must not have experienced treatment failure with eculizumab (*see definitions below); and
- Re-assessments must be undertaken at least every 6 months to evaluate whether treatment should be continued.

*A treatment response is defined as:

I. Normalisation of haematological parameters as demonstrated by **at least two** of the following: (a) platelet count, (b) haptoglobin, (c) lactate dehydrogenase (LDH); and
II. **One** of the following:
   (a) An increase in eGFR of >25% from baseline, where the baseline is the eGFR measurement immediately prior to commencing treatment with a complement C5 inhibitor;
   (b) An eGFR within +/- 25% from baseline;
   (c) An avoidance of dialysis-dependence but worsening of kidney function with a reduction in eGFR ≥25% from baseline.

*A treatment failure is defined as:

I. Being dialysis-dependent and have failed to demonstrate significant resolution of extra-renal complications if originally presented; or
II. Being on dialysis and have been on dialysis for 4 months of the previous 6 months while receiving a complement C5 inhibitor, and have failed to demonstrate significant resolution of extra-renal complications if originally presented.

2) As monotherapy for aHUS in adults and children who are switching from another complement inhibitor to eculizumab.

- Patient must have a diagnosis of aHUS; and
- Patient requires a switch to eculizumab treatment due to reasons such as, but not limited to, pregnancy, planning pregnancy, or the previous complement inhibitor treatment is not included on the MOH List of Subsidised Drugs; and
- Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of aHUS.

For continuation of treatment:

- After patient has received eculizumab for at least 3 - 6 months, patient must have demonstrated on-going treatment response and must not have experienced treatment failure with eculizumab (*see definitions provided under indication #1); and
- Re-assessments must be undertaken at least every 6 months to evaluate whether treatment should be continued.

3) **As monotherapy for aHUS in adults and children who experience a relapse after discontinuing complement C5 inhibitor therapy.**
   - Patient must have been previously diagnosed with aHUS; and
   - Patient must have demonstrated treatment response and must not have experienced treatment failure with a complement C5 inhibitor (*see definitions provided under indication #1); and
   - Patient must have the following clinical conditions prior to recommencing eculizumab treatment:
     (a) Significant haemolysis (as measured by low/absent haptoglobin, or presence of schistocytes on the blood film, or LDH above normal); and
     (b) **One** of the following:
       - Platelet count <150 x 10^9/L or ≥25% decrease from baseline platelet count;
       - TMA-related organ damage or impairment; and
   - Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of aHUS.

   For continuation of treatment:
   - After patient has received eculizumab for at least 3 - 6 months, patient must have demonstrated on-going treatment response and must not have experienced treatment failure with eculizumab (*see definitions provided under indication #1); and
   - Re-assessments must be undertaken at least every 6 months to evaluate whether treatment should be continued.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

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The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

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Find out more about ACE at www.ace-hta.gov.sg/about

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