

## 5.11 PEGCETACOPLAN, Solution for subcutaneous infusion, 1,080 mg in 20 mL, Empaveli™, Swedish Orphan Biovitrum Australia Pty Ltd

### 1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100, Authority Required listing for pegcetacoplan for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH) who have inadequate clinical response to C5 inhibitor treatment.
- 1.2 Listing was requested on the basis of a clinical comparison of pegcetacoplan versus eculizumab, a cost-effectiveness analysis versus ravulizumab (using eculizumab's clinical data as a proxy) and financial estimates assuming that ravulizumab will be PBS-listed and eculizumab would remain on the Life Saving Drugs Program (LSDP). This was inconsistent with the July 2021 PBAC outcome for ravulizumab which also recommended that eculizumab be moved from the LSDP to the PBS (para 7.2, ravulizumab public summary document (PSD), July 2021 PBAC meeting).

**Table 1: Key components of the clinical issue addressed in the submission**

| Component      | Description  |
|----------------|--|
| Population     | Patients with paroxysmal nocturnal haemoglobinuria (PNH) and inadequate clinical response to C5 inhibitor treatment (haemoglobin level <10.5 g/dL after ≥3 months of stable treatment) |
| Intervention   | Pegcetacoplan 1,080 mg in 20 mL twice weekly subcutaneous infusion via a commercially available infusion pump <sup>a</sup>   |
| Comparators    | Eculizumab 900 mg every 2 weeks intravenous infusion (maintenance dose) and ravulizumab 3,300 mg every 8 weeks intravenous infusion (maintenance dose)                                 |
| Outcomes       | Improved haemoglobin level and transfusion avoidance, leading to improvements in quality of life   |
| Clinical claim | Pegcetacoplan is superior in terms of improvements in haemoglobin level and at least non-inferior in terms of efficacy and safety compared to eculizumab and ravulizumab               |

Source: Table 1-1, p 13 of the submission

<sup>a</sup> Dosing frequency may be increased to 1,080 mg every third day if a patient's lactate dehydrogenase (LDH) level is greater than 2 x upper limit of normal (ULN)

### 2 Background

#### Registration status

- 2.1 Pegcetacoplan was submitted under the TGA/PBAC parallel process. During the evaluation the TGA Delegate's overview became available. The TGA approved the registration of pegcetacoplan on 28 January 2022.
- 2.2 The approved TGA indication is as follows:

‘EMPAVELI is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have an inadequate response to, or are intolerant of, a C5 inhibitor’.

- 2.3 The product information indicates that pegcetacoplan is to be included in the Black Triangle Scheme and includes a boxed warning regarding the risk of serious infections caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B (HIB), with recommendations to vaccinate against these bacteria prior to initiation of pegcetacoplan treatment. The ESC noted that ATAGI advice was required to extend access on the National Immunisation Program (NIP) to these vaccines for this purpose. The PBAC noted ATAGI advice dated 3 March 2022 which stated it would be reasonable to recommend vaccination prior to pegcetacoplan including against *S. pneumoniae*; *N. meningitidis* A, C, W, Y, and B; and *H. influenzae*. If the therapy is ongoing, noting some treatment courses can be months/years, this will lead to persistent complement deficiency, so ongoing vaccination will be required to provide ongoing protection from these encapsulated bacteria. The ATAGI advice stated the required number of vaccines would be:

- HIB – single dose
- Conjugate pneumococcal vaccine (PCV13) single dose
  - PPV23 max 2 doses (1st at min 8-weeks following PCV13); 2nd min 4 years later
- Men ACWY- single dose with a booster recommended every 5 years
- Men B vaccine: 2 doses minimum 8-weeks apart
  - Booster dose 3-years after the previous dose if aged  $\leq 6$  years at completion of primary course and at 5 years after the previous dose if aged  $\geq 7$  years at completion of primary

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

### **3 Requested listing**

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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| MEDICINAL PRODUCT<br>medicinal product pack   | PBS item<br>code | Max. qty<br>packs | Max. qty<br>units | No. of<br>Rpts | Dispensed price<br>for maximum<br>quantity | Available brands    |
|---|------------------|-------------------|-------------------|----------------|--|---------------------|
| PEGCETACOPLAN   |                  |                   |                   |                |  |                     |
| Pegcetacoplan 1,080 mg/20 mL;<br>20 mL  | NEW              | 1                 | 18                | 0              | \$<br>published price                      | Empaveli<br>SOBI AU |
| <b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program (Public and Private)  |                  |                   |                   |                |  |                     |
| <b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners   |                  |                   |                   |                |  |                     |
| <b>Restriction type:</b><br><input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic submission)  |                  |                   |                   |                |  |                     |
| <b>Indication:</b> Paroxysmal nocturnal haemoglobinuria (PNH)   |                  |                   |                   |                |  |                     |
| <b>Treatment Phase:</b> Initial treatment   |                  |                   |                   |                |  |                     |
| <b>Clinical criteria:</b><br><i>Patient must not have received prior treatment with this drug for this condition.</i>   |                  |                   |                   |                |  |                     |
| <b>AND</b>  |                  |                   |                   |                |  |                     |
| <b>Clinical criteria:</b><br>Patient must have a haemoglobin level of less than 10.5 g/dL   |                  |                   |                   |                |  |                     |
| <b>AND</b>  |                  |                   |                   |                |  |                     |
| <b>Clinical criteria:</b><br>Patient must be receiving supply of eculizumab under the Australian Government's LSDP eligibility criteria for this condition for at least 3 months, OR<br>Patient must be receiving supply of ravulizumab under the PBS for this condition for at least 3 months<br><i>Patient must have received treatment with a C5 inhibitor for at least 3 months before initiating treatment with this drug.</i>   |                  |                   |                   |                |  |                     |
| <b>AND</b>  |                  |                   |                   |                |  |                     |
| <b>Clinical criteria:</b><br><i>The treatment must be in combination with a PBS-subsidised C5 inhibitor for a period of 4 weeks during initiation of therapy.</i>   |                  |                   |                   |                |  |                     |
| <b>Treatment criteria:</b><br>Must be treated by a haematologist or in consultation with a haematologist; OR<br>Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details<br><del>Patient or carer of patient may self-administer pegcetacoplan on the basis that the haematologist deems it appropriate and that the patient or carer or patient complete training on subcutaneous injection by a suitable health care professional.</del> |                  |                   |                   |                |  |                     |
| <b>Population criteria:</b><br>Patients must be aged 18 years or older  |                  |                   |                   |                |  |                     |
| <b>Prescribing Instructions:</b> <i>At the time of the authority application, medical practitioners should request the appropriate number of vials for one months supply as per the Product Information.</i>  |                  |                   |                   |                |  |                     |
| <b>Prescribing Instructions:</b> <i>C5 inhibitor defined as eculizumab or ravulizumab</i>   |                  |                   |                   |                |  |                     |
| <b>Prescribing Instructions:</b><br><i>At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:</i><br>(i) Haemoglobin (g/L)<br>(ii) Platelets (x109/L)<br>(iii) White Cell Count (x109/L)<br>(iv) Reticulocytes (x109/L)<br>(v) Neutrophils (x109/L)<br>(vi) Granulocyte clone size (%)<br>(vii) Lactate Dehydrogenase (LDH) and the upper limit of normal (ULN) for the reporting laboratory<br>(viii) Multiple of LDH ULN      |                  |                   |                   |                |  |                     |
| <b>Administrative advice:</b><br>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).<br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>  |                  |                   |                   |                |  |                     |

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Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at [www.servicesaustralia.gov.au/hpos](http://www.servicesaustralia.gov.au/hpos)  
 Or mailed to:  
 Services Australia  
 Complex Drugs  
 Reply Paid 9826  
 HOBART TAS 7001

**Administrative advice:** No increase in the maximum number of repeats may be authorised.

**Caution:**  
 WARNING: This drug increases the risk of encapsulated bacterial infections.  
 Consult the approved PI for information about vaccination against meningococcal, pneumococcal and *Haemophilus influenzae* type B (Hib) infection.

| MEDICINAL PRODUCT<br>medicinal product pack  | PBS item<br>code | Max. qty<br>packs | Max. qty units | No. of<br>Rpts | Dispensed price<br>for maximum<br>quantity | Available<br>brands |
|--|------------------|-------------------|----------------|----------------|--|---------------------|
| PEGCETACOPLAN  |                  |                   |                |                |  |                     |
| Pegcetacoplan 1,080 mg/20 mL; 20 mL  | NEW              | 1                 | 18             | 5              | \$<br>published price                      | Empaveli<br>SOBI AU |
| <b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program ( <i>Public and Private</i> )  |                  |                   |                |                |  |                     |
| <b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners  |                  |                   |                |                |  |                     |
| <b>Restriction type:</b><br><input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic submission)   |                  |                   |                |                |  |                     |
| <b>Indication:</b> Paroxysmal nocturnal haemoglobinuria (PNH)  |                  |                   |                |                |  |                     |
| <b>Treatment Phase:</b> Continuing treatment   |                  |                   |                |                |  |                     |
| <b>Clinical criteria:</b><br><del>Patient must not be currently participating in a clinical trial.</del>   |                  |                   |                |                |  |                     |
| <b>Clinical criteria:</b><br><i>Patient must have had PBS-subsidised treatment with this drug for this condition under the initial treatment phase.</i>  |                  |                   |                |                |  |                     |
| <b>AND</b>   |                  |                   |                |                |  |                     |
| <b>Clinical criteria:</b><br><del>Patient must have demonstrated clinical improvement or stabilisation of condition based on clinical data on the following monitoring requirements provided every 12 months</del>   |                  |                   |                |                |  |                     |
| <b>AND</b>   |                  |                   |                |                |  |                     |
| <b>Clinical criteria:</b><br>The treatment must not be in combination with a PBS-subsidised C5 inhibitor   |                  |                   |                |                |  |                     |
| <b>Treatment criteria:</b><br>Must be treated by a haematologist <del>or in consultation with a haematologist;</del> <b>OR</b><br>Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details  |                  |                   |                |                |  |                     |
| <del>AND The treatment must be the sole PBS subsidised treatment for this condition<br/>                     Patient or carer of patient may self-administer pegcetacoplan on the basis that the haematologist deems it appropriate and that the patient or carer or patient complete training on subcutaneous injection by a suitable health care professional.</del> |                  |                   |                |                |  |                     |
| <b>Population criteria:</b><br>Patients must be aged 18 years or older   |                  |                   |                |                |  |                     |
| <b>Prescribing Instructions:</b> <i>At the time of the authority application, medical practitioners should request the appropriate number of vials for one months supply as per the Product Information.</i>   |                  |                   |                |                |  |                     |
| <b>Prescribing Instructions:</b> <i>C5 inhibitor defined as eculizumab or ravulizumab</i>  |                  |                   |                |                |  |                     |
| <b>Prescribing Instructions:</b> <i>At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:</i>   |                  |                   |                |                |  |                     |
| (i) Haemoglobin (g/L)  |                  |                   |                |                |  |                     |
| (ii) Platelets (x109/L)  |                  |                   |                |                |  |                     |

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|        |  |
|--------|--|
| (iii)  | White Cell Count (x109/L)  |
| (iv)   | Reticulocytes (x109/L)   |
| (v)    | Neutrophils (x109/L)   |
| (vi)   | Granulocyte clone size (%)   |
| (vii)  | Lactate Dehydrogenase (LDH) and the upper limit of normal (ULN) for the reporting laboratory |
| (viii) | Multiple of LDH ULN  |

**Administrative advice:**

Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at [www.servicesaustralia.gov.au](http://www.servicesaustralia.gov.au)

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Or mailed to:

Services Australia

Complex Drugs

Reply Paid 9826

HOBART TAS 7001

**Administrative advice:** No increase in the maximum number of repeats may be authorised.

**Caution:**

WARNING: This drug increases the risk of encapsulated bacterial infections.

Consult the approved PI for information about vaccination against meningococcal, pneumococcal and *Haemophilus influenzae* type B (Hib) infection.

**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public and Private)

**Prescriber type:**  Medical Practitioners

**Restriction type:**

Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic submission)

**Indication:** Paroxysmal nocturnal haemoglobinuria (PNH)

**Treatment Phase:** Grandfathered Treatment

**Clinical criteria:**

Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to availability on the PBS [listing date]

**AND**

**Clinical criteria:**

The treatment must be the sole PBS-subsidised treatment for this condition

**AND**

**Clinical criteria:**

Patient must have had a haemoglobin level of less than 10.5 g/dL prior to initiating non-PBS-subsidised treatment with this drug

**AND**

**Clinical criteria:**

Patient must have been receiving treatment with a C5 inhibitor for at least 3 months before initiating treatment with this drug

**AND**

**Clinical criteria:**

Patient must have stable or responding disease

**AND**

**Clinical criteria:**

Patient must have demonstrated clinical improvement or stabilisation of condition while receiving treatment with this drug for this condition based on clinical data on the following monitoring requirements provided every 12 months

**Treatment criteria:**

Must be treated by a haematologist; **OR**

Must be treated by a non-specialist medical physician who has consulted a haematologist on the patient's drug treatment details

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|   |
|---|
| <b>Population criteria:</b>   |
| Patients must be aged 18 years or older   |
| <b>Prescribing Instructions:</b> At the time of the authority application, medical practitioners should request the appropriate number of vials for one months supply as per the Product Information.   |
| <b>Prescribing Instructions:</b> C5 inhibitor defined as eculizumab or ravulizumab  |
| <b>Prescribing Instructions:</b> At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:   |
| <ul style="list-style-type: none"> <li>(i) Haemoglobin (g/L)</li> <li>(ii) Platelets (x109/L)</li> <li>(iii) White Cell Count (x109/L)</li> <li>(iv) Reticulocytes (x109/L)</li> <li>(v) Neutrophils (x109/L)</li> <li>(vi) Granulocyte clone size (%)</li> <li>(vii) Lactate Dehydrogenase (LDH) and the upper limit of normal (ULN) for the reporting laboratory</li> <li>(viii) Multiple of LDH ULN</li> </ul> |
| <b>Administrative advice:</b>   |
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| Or mailed to:   |
| Services Australia  |
| Complex Drugs   |
| Reply Paid 9826   |
| HOBART TAS 7001   |
| <b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.   |
| <b>Note</b>   |
| Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing Treatment' criteria.  |
| <b>Caution:</b>   |
| <b>WARNING:</b> This drug increases the risk of encapsulated bacterial infections.  |
| Consult the approved PI for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection.  |

3.2 The submission requested an Authority Required listing, under the Section 100 – HSD (Public/Private hospital) Program for the initial and grandfathering restrictions, and Section 100 – HSD (Community Access) Program for the continuing restriction. The assumption that patients would receive initial treatment in a hospital setting was appropriate, however, the method of administration for pegcetacoplan is complex and it is unclear what proportion of patients would self-administer treatment following the initial phase. The ESC noted the pre-subcommittee response (PSCR) advised that feedback from trial participants has been supportive of self-administration. The PBAC advised that PNH was managed by highly specialised haematologists and considered that the pegcetacoplan restriction should align with eculizumab and ravulizumab as a Section 100 – HSD (Public/Private hospital) Program listing and written authority. The PBAC noted the product is primarily intended to be administered in the home setting by the patient or caregiver after initial treatment.

The PBAC noted that Complex Authority Required (CAR) drugs, such as eculizumab or ravulizumab, can also be dispensed by an approved s90 Community Pharmacy and considered a similar listing for pegcetacoplan should not be a barrier to self-administration.

- 3.3 The sponsor proposed that pegcetacoplan be listed at [REDACTED] [REDACTED] with ravulizumab and/or eculizumab. The proposed price was calculated based on the [REDACTED] on the PBS, as a proxy for the published price of eculizumab for PNH. The sponsor indicated it is willing, in principle, to enter into a Special Pricing Arrangement to align with the confidential effective price of eculizumab and ravulizumab should they be listed on the PBS for PNH.
- 3.4 To ensure no additional cost is associated with patients switching from C5 inhibitor treatment to pegcetacoplan, the sponsor proposed a [REDACTED] % price rebate (via Special Pricing Arrangement) for the initial 4-week treatment phase when pegcetacoplan is co-administered with a C5 inhibitor treatment.
- 3.5 The sponsor also proposed provision of the infusion pumps and monthly consumables to individual patients at no additional cost via a patient support program (described in the Quality Use of Medicines section below).
- 3.6 The proposed quantity in the essential elements allows for a maximum of [REDACTED] vials to be supplied to patients with each script. It may be appropriate to consider flexible rather than fixed quantities for the proposed initial and continuing restrictions, with potential flow-on consequences to the proposed rebate for the run-in period. In the current PBS listing for eculizumab for aHUS, medical practitioners must request the appropriate number of vials to provide sufficient drug for 4 weeks and up to 5 repeats according to the specified dosage in the product information.
- 3.7 The requested restriction is for second-line therapy in patients with a Hb level of <10.5 g/dL despite C5 inhibitor treatment. The proposed restriction appeared narrower than the TGA indication for the treatment of adult patients with PNH who have an inadequate response, or are intolerant of, a C5 inhibitor; the ESC considered it would be reasonable for the PBS listing to include patients who are intolerant to C5 inhibitors to align with the TGA indication. The pre-PBAC response stated the sponsor was willing to update the proposed restriction wording to include these patients.
- 3.8 The proposed clinical criteria were less specific than trial eligibility criteria, which specified that the dose of eculizumab should be stable for at least 3 months. The criteria were broad and may include patients who are failing C5 inhibitor treatment. The ESC noted more clarity was required regarding how patients would be able to continue accessing therapy with eculizumab or ravulizumab during the 4-week initiation phase (co-administration of pegcetacoplan and a C5 inhibitor), depending on continuation criteria should they be listed on the PBS. This may be less of an issue for patients treated with ravulizumab (dosed every 8 weeks), with the submission claiming that patients should initiate pegcetacoplan at 4 weeks after their last

ravulizumab dose. The PBAC considered that with PBS listing of C5 inhibitors, ravulizumab would become the treatment of choice for patients and clinicians.

- 3.9 The clinical criteria for continuing treatment were based on the current guidelines for the treatment of PNH through the LSDP and proposed continuing criteria for ravulizumab for the treatment of PNH on the PBS. The submission stated that the sponsor is willing to work with the PBAC and Restrictions Working Group to refine treatment response criteria, which could include clinical and laboratory markers. The PBAC advised continuation criteria for pegcetacoplan should be aligned with eculizumab and ravulizumab if they are listed on the PBS.
- 3.10 No data were available in patients with higher body weights (BMI  $\geq 35$  kg/m<sup>2</sup>) as they were excluded from the key trial. The evaluation considered it may be appropriate to include weight restrictions given the lack of efficacy and safety data and potential for lower pegcetacoplan exposure in these patients using the recommended fixed doses. The PBAC considered that it was reasonable for the restriction to remain silent on BMI, given small numbers of patients and limited access to effective treatment.
- 3.11 In the economic model, the submission assumed that patients discontinuing pegcetacoplan would resume treatment with ravulizumab. It was unclear whether the final listing arrangements for eculizumab and ravulizumab would allow for resumption of treatment and how that would interact with continuing restrictions requiring demonstration of treatment response. The PBAC advised that pegcetacoplan patients would need to be able go back onto a C5 inhibitor if they were non-responders (a one-off) and for pregnancy (with the option to return pegcetacoplan postpartum, unless they were a non-responder). Multiple switches for pregnancy should be allowed.
- 3.12 The submission stated that the sponsor is planning to establish a patient access program for pegcetacoplan, prior to PBS listing of pegcetacoplan. The sponsor requested grandfathering provisions for these patients. It was unclear whether these patients would meet the eligibility criteria under the proposed PBS listing.
- 3.13 The submission stated that there were < 500 patients currently receiving pegcetacoplan, and up to < 500 patients would require grandfathering at the time of PBS listing. The proposed clinical criteria specify that patients must have stable or responding disease and demonstrate clinical stabilisation of the condition based on annual monitoring requirements. No clear definition of treatment response was provided in the submission. It is likely that the same measures of response used in the continuing restriction would also apply to the grandfathering restriction. The PBAC considered the inclusion of a grandfathering restriction was appropriate.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 PNH is a rare, chronic blood condition in which red blood cells are attacked by the body's immune system. It is an acquired condition, meaning it is not inherited so cannot be passed on from parent to child, and is most frequently diagnosed between the ages of 30-40 years old. It is characterised by intravascular haemolysis (rupturing of red blood cells) with resultant anaemia that can lead to transfusion dependence, severe disabling symptoms of haemolysis (e.g. pain, organ dysfunction) and thrombosis (blood clotting). PNH can also lead to extravascular haemolysis occurring in the liver, spleen, bone marrow and lymph nodes. Thromboembolic events due to blood clots obstructing blood vessels are the leading cause of premature death in patients with PNH.
- 4.2 The severity of PNH is variable and not all patients require active complement inhibitor therapy. Patients with less severe disease can be treated with supportive therapies including folic acid and iron tablets, while patients with more severe disease may require red blood cell transfusions and anticoagulants. Life-long treatment is required. There is potential for cure with allogeneic stem cell transplantation, but this is rarely used as it is associated with a high level of morbidity and mortality.
- 4.3 The proposed PNH patient population in the submission is aligned with the classic PNH patient population who are eligible to receive eculizumab and ravulizumab. The submission targeted patients who have inadequate clinical response (defined as haemoglobin levels less than 10.5 g/dL) despite stable treatment with C5 inhibitors for at least 3 months.
- 4.4 Pegcetacoplan is a C3 complement inhibitor that acts proximally in the complement cascade to control both C3b-mediated extravascular haemolysis, and downstream terminal complement-mediated intravascular haemolysis. The regimen starts with a 4-week run-in period where it is co-administered with the patient's current C5 inhibitor treatment regimen. After 4 weeks, the C5 inhibitor treatment is ceased, and patients continue with pegcetacoplan monotherapy. The recommended dose is 1,080 mg twice weekly, which may be increased to 1,080 mg every third day if a patient has a lactate dehydrogenase (LDH) level greater than 2 x upper limit of normal (ULN).
- 4.5 Pegcetacoplan should only be administered as a SC infusion using a syringe system infusion pump that can deliver doses up to 20 mL. The method of administration and instructions for use appear complex, which may lead to potential issues with safety and treatment compliance particularly for patients who choose to self-administer. The ESC noted an objective of the proposed patient support program is to provide sufficient training in self-administration (see Quality Use of Medicines).
- 4.6 The clinical management algorithm positioned pegcetacoplan as second-line therapy in patients with inadequate response to C5 inhibitor treatment in addition to best

supportive care. The definition of inadequate response was broad, with the following treatment settings proposed for pegcetacoplan in the submission:

- An alternative to higher doses of eculizumab, in patients with persistent haemolysis despite treatment with C5 inhibitors. The submission noted potential causes including rare cases of genetic resistance to eculizumab treatment and breakthrough haemolysis due to the pharmacokinetics (or underdosing) of eculizumab (10-15% of patients). However, the submission acknowledged that access to eculizumab dose increases was generally not allowed under the LSDP. In July 2021, the PBAC considered that a PBS listing for eculizumab should address the difference in maintenance dosing interval of 14 days on the LSDP and 14 days  $\pm$  2 days in the product information (para 7.5, ravulizumab Public Summary Document [PSD], July 2021 PBAC meeting).
- An alternative to splenectomy or bone marrow transplant in patients with severe, treatment refractory disease defined as those who continue to experience unacceptable levels of haemolysis and/or risk of thrombosis. The submission claimed that use of pegcetacoplan may prevent the need for such later line therapies.

- 4.7 The clinical relevance of low Hb levels as a single measure of inadequate response was not explicitly discussed in the submission. In the pegcetacoplan key trial, PEGASUS, transfusions were administered in patients with Hb <7.0 g/dL without symptoms or <9.0 g/dL with symptoms. The PBS eligibility criteria for PNH treatment defines anaemia as chronic/recurrent where other causes of haemolysis have been excluded and demonstrated by more than one measure of Hb  $\leq$ 70 g/L (i.e.  $\leq$ 7.0 g/dL) without anaemic symptoms or  $\leq$ 100 g/L (i.e.  $\leq$ 10.0 g/dL) with concurrent anaemic symptoms.
- 4.8 The submission claimed that patients who currently have suboptimal haematological outcomes would persist with C5 inhibitor treatment as these treatments would still adequately manage the life-threatening aspects of their disease. The submission stated that treatment cessation would only occur in clear cases of non-response, for example, in patients who are treatment resistant. The PBAC agreed with the ESC that this assumption was reasonable in the absence of other treatments for PNH.
- 4.9 Overall, the role of pegcetacoplan in the Australian setting was unclear. While treatment with pegcetacoplan may benefit patients with suboptimal haematological response to C5 inhibitors, there is a lack of long-term outcomes including thrombosis and survival.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The submission nominated both eculizumab and ravulizumab as comparators. In July 2021, the PBAC recommended eculizumab be moved from the LSDP to a listing on the

PBS at a reduced price and that ravulizumab be listed on a cost-minimisation basis to eculizumab (para 7.1, ravulizumab PSD, July 2021 PBAC meeting).

- 5.2 Both eculizumab and ravulizumab are relevant comparators as C5 inhibitors are the only active treatment options currently available for PNH. However, the cost-effectiveness of C5 inhibitors in patients who have suboptimal haematological response despite treatment with C5 inhibitors has not been assessed. The ESC considered eculizumab and ravulizumab to be the most appropriate comparators as they will be replaced with pegcetacoplan in clinical practice in patients with an inadequate response to a C5 inhibitor.
- 5.3 During the evaluation, it was noted that there are multiple therapies for PNH in late-stage development including eculizumab biosimilars (BCD-148, SB-12, ABP-959), a subcutaneous formulation of ravulizumab, a novel subcutaneous C5 inhibitor (crovalimab), and oral inhibitors of complement factor D (danicopan) and factor B (iptacopan). The status of these drugs in the Australian setting was unknown and therefore these therapies were not considered further during evaluation.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, the existing unmet clinical need despite the availability of C5 inhibitors, how the drug would be used in practice as well as the delivery device. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments from an individual who has used this medicine described the benefits of treatment with pegcetacoplan including the ability to return to work, improvements in quality of life and a reduction in blood transfusions. Comments from the PNH Support Association of Australia describe the importance of this medicine in reducing hospital attendance for treatment, of being able to self-administer the infusion at home and the potential for greater flexibility with travel as a result. The comments from a health care professional described the clinical need for pegcetacoplan along with benefits such as reduced fatigue and need for transfusions.

### **Clinical trials**

- 6.3 The submission was based on a head-to-head trial (PEGASUS) comparing pegcetacoplan with eculizumab in patients with PNH who have low Hb level <10.5 g/dL despite treatment with stable doses of eculizumab for at least 3 months.
- 6.4 A supportive indirect comparison of pegcetacoplan and ravulizumab based on the pegcetacoplan trial (PEGASUS) and ravulizumab trial (Trial 302), with eculizumab as a common reference was also presented in the submission. The submission claimed that due to significant issues in transitivity between PEGASUS and Trial 302, and the inability to adjust for clinically relevant baseline characteristics, the results of the matching adjusted indirect comparison (MAIC) of pegcetacoplan and ravulizumab are subject to serious risk of bias and may not be informative for decision-making. The evaluation considered the submission's claim was reasonable given the trial population in PEGASUS was those who had suboptimal haematological response despite eculizumab treatment and the population in Trial 302 was those who were clinically stable with eculizumab treatment based on LDH level and no recent major adverse vascular event (i.e. suboptimal responders vs responders). Baseline characteristics suggest patients in the PEGASUS trial had lower Hb levels and higher rates of transfusion compared to those in Trial 302 (the majority of Trial 302 patients were transfusion independent). In addition, the eculizumab arm in the PEGASUS trial allowed for higher doses whereas patients in the eculizumab arm of Trial 302 were only allowed standard dose eculizumab.
- 6.5 Trial 302 has previously been considered by the PBAC during the July 2020 and July 2021 considerations of ravulizumab for PNH.
- 6.6 The ESC noted ravulizumab is a pharmacological analogue of eculizumab and the PBAC had previously considered ravulizumab as non-inferior in effectiveness and safety compared to eculizumab, based on Trials 301 (treatment naïve) and 302 (previously stable on treatment with eculizumab) (ravulizumab PSD, July 2021 PBAC meeting). The ESC considered the comparative results from the PEGASUS trial between pegcetacoplan and eculizumab would likely be indicative of comparative effectiveness and safety between pegcetacoplan and ravulizumab.
- 6.7 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials and associated reports presented in the submission**

| Trial ID  | Protocol title/ Publication title  | Publication citation   |
|---|--|--|
| <b>Pegcetacoplan vs eculizumab</b>                          |  |  |
| PEGASUS<br>(APL2-302,<br>NCT03500549)                       | A Phase 3, Randomized, Multicenter, Open-label, Active-comparator Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH). PEGASUS Clinical Trial Protocol.   | May 2020   |
|   | A Phase 3, Randomized, Multicenter, Open-label, Active-comparator Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH). Week 16 Analysis.  | May 2020   |
|   | A Phase 3, Randomized, Multicenter, Open-label, Active-comparator Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH). Week 48 Analysis.  | April 2021   |
|   | Hillmen P, Szer J, Weitz I et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria.  | New England Journal of Medicine<br>2021;384(11):1028-37  |
| <b>Ravulizumab vs eculizumab</b>                            |  |  |
| Trial 302<br>(NCT03056040)                                  | Kulasekararaj AG, Hill A, Rottinghaus ST et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study.<br>Kulasekararaj AG, Hill A, Langemeijer S et al. One-year outcomes from a phase 3 randomized trial of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria who received prior eculizumab.<br>Brodsky RA, Peffault de Latour R, Rottinghaus ST et al. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. | Blood 2019;133(6):540-9<br><br>European journal of haematology<br>2021;106(3):389-97<br>Haematologica<br>2021;106(1):230-7 |
| <b>Indirect comparison of pegcetacoplan and ravulizumab</b> |  |  |
| Bhak 2020   | Bhak RH, Mody-Patel N, Baver SB et al. Comparative effectiveness of pegcetacoplan versus ravulizumab in patients with paroxysmal nocturnal hemoglobinuria previously treated with eculizumab: a matching-adjusted indirect comparison.   | Current Medical Research and Opinion 2021;<br>37(11):1913-23   |

Source: Table 2-3, p 39 and Table 2-4, p 43 of the submission

Note: There were multiple citations related to the PEGASUS trial and Trial 302 (abstracts and/or poster presentations) that were not included in the table above. The full lists are presented in Table 2-3, p 39 and Table 2-4, p 43 of the submission.

6.8 The key features of the PEGASUS trial are summarised in the table below.

**Table 3: Key features of the included evidence**

| Trial                              | N  | Design/ duration   | Risk of bias | Patient population   | Outcomes  | Use in modelled evaluation   |
|------------------------------------|----|--|--------------|--|---|--|
| <b>Pegcetacoplan vs eculizumab</b> |    |  |              |  |   |  |
| PEGASUS                            | 80 | MC, R, OL, active controlled trial (4-week run-in, 16-week RCP, 32-week OLP) | High         | Adults with PNH who were receiving eculizumab at a stable dose for ≥3 months prior, but continued to have haemoglobin (Hb) levels <10.5 g/dL | Hb level, transfusion avoidance, ARC, LDH, FACIT-Fatigue score, EORTC QLQ-C30 | Age, gender, weight, pegcetacoplan treatment utilisation pattern, re-analysis of individual patient data for transfusion status and Hb level, treatment discontinuations, iron chelation therapy utilisation, EORTC QLQ-C30 scores, RBC units transfused and adverse events. |

Source: Sections 2.4.1 to 2.4.3, pp 50-61 of the submission

Abbreviations: ARC, absolute reticulocyte count; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; MC, multi-centre; OL, open label; OLP, open label period; R, randomised; RCP, randomised controlled period

- 6.9 Although the key trial had an open-label design, the majority of outcome measures were laboratory-assessed and unlikely to be affected by blinding. However, awareness of treatment assignment may have affected the reporting of subjective patient outcomes (e.g. safety, quality of life) and disease management (e.g. use of supportive treatments including blood transfusion).
- 6.10 There was differential discontinuation during the randomised controlled period (pegcetacoplan, 7.3%; eculizumab, 0%) and open label pegcetacoplan period (pegcetacoplan/pegcetacoplan, 7.9%, eculizumab/pegcetacoplan, 17.9%). All except 1 discontinuation were due to adverse events. Clinical data were not collected following discontinuation, which may have an impact on any differences observed between treatment arms after these patients discontinued.
- 6.11 There were high proportions of patients with documented major protocol deviations during the randomised period (pegcetacoplan, 71%; eculizumab, 77%) and open label period (32.5%). The majority of these deviations was due to non-compliance with study assessment/schedule.
- 6.12 The trial eligibility criteria for pegcetacoplan were broad (based on low Hb level and prior treatment with C5 inhibitors only) but appeared to recruit patients who were clinically stable, treated with stable doses of eculizumab over a mean duration of 5 years. Less than a third of patients had a prior history of thrombosis and none had a major adverse vascular event in the 6 months prior to enrolment. Overall, 25% of the trial population had no transfusions in the prior year, 20% had one to three transfusions and 55% had four or more transfusions. It is unclear whether the disease burden of the trial population is representative of the proposed Australian population. The magnitude of benefit of pegcetacoplan in patients with more severe or treatment refractory disease is unknown.
- 6.13 The trial excluded patients with a BMI of  $\geq 35$  kg/m<sup>2</sup> based on pharmacokinetic modelling data that indicated lower drug exposure in patients with class II or greater obesity. The efficacy and safety of pegcetacoplan in patients with a BMI of  $\geq 35$  kg/m<sup>2</sup> is unknown. No contraindication or special warning regarding BMI was included in the draft product information.
- 6.14 In the trial, all patients received pegcetacoplan in addition to their current regimen of eculizumab for 4 weeks prior to randomisation. It was unclear whether the observed results in the eculizumab arm following the introduction and abrupt withdrawal of pegcetacoplan are applicable to patients who are otherwise stable on eculizumab monotherapy in practice.
- 6.15 There are currently no long-term studies of disease-related complications and survival in patients treated with pegcetacoplan, beyond the short-term haematological outcomes data from the 16-week randomised control period and additional 32-week open label pegcetacoplan period of the PEGASUS trial.

### Comparative effectiveness

6.16 As per trial protocol, the main statistical analyses for key outcomes (laboratory measures and patient-reported outcomes) were censored for transfusion as RBC transfusions may confound the efficacy results. This approach may limit the robustness of results based on the censored dataset due to the small number of transfusion-free patients in the eculizumab arm informing results at the end of the randomised controlled period (N=6). Results based on the uncensored dataset for the key outcomes were also presented in the submission.

6.17 Results for transfusion avoidance during the 16-week randomised controlled period of the trial is presented in the table below.

**Table 4: Proportion of patients avoiding transfusions through Week 16 (ITT)**

|   | Pegcetacoplan<br>n/N (%) | Eculizumab<br>n/N (%) | Risk difference (95%<br>CI) |
|---|--------------------------|-----------------------|-----------------------------|
| No transfusion                              | 35/41 (85.4)             | 6/39 (15.4)           | 62.5 (48.3, 76.8)           |
| - Received ≥1 transfusion                   | 5/41 (12.2)              | 33/39 (84.6)          | -                           |
| - Withdrew from study without a transfusion | 1/41 (2.4)               | 0                     | -                           |

Source: Table 2-21, p 70 of the submission

Abbreviation: CI, confidence interval

6.18 For transfusion avoidance, the lower bound of the 95% confidence interval was greater than the protocol-specified non-inferiority margin of -20%, indicating that pegcetacoplan was noninferior to eculizumab. The submission acknowledged the lack of formal statistical testing for superiority due to the failure in the hierarchical testing of non-inferiority of key secondary outcomes (see LDH outcome below). However, the submission claimed the results indicated a much greater proportion of patients treated with pegcetacoplan avoided transfusions compared to those receiving eculizumab. The results should be interpreted with caution due to the lack of blinding; in particular, fewer patients in the eculizumab arm were transfusion free during the 16-week randomised controlled period compared to baseline (25% had no transfusions in the 12 months prior).

6.19 Results for the outcomes of change in Hb level (g/dL), reticulocyte count, LDH, and FACIT-Fatigue score during the 16-week randomised controlled period of the trial are presented in the table below.

**Table 5: Change in Hb, reticulocyte count, LDH and FACIT-Fatigue score (censored for transfusion, ITT)**

| Analysis                        | Pegcetacoplan (N=41) |                    |                          | Eculizumab (N=39)  |                    |                          | Difference (95% CI) <sup>a</sup> |
|---------------------------------|----------------------|--------------------|--------------------------|--------------------|--------------------|--------------------------|----------------------------------|
|                                 | Baseline mean (SD)   | Endpoint mean (SD) | Change (SE) <sup>a</sup> | Baseline mean (SD) | Endpoint mean (SD) | Change (SE) <sup>a</sup> |                                  |
| Hb level (g/dL)                 | 8.69 (1.08)          | 11.65 (1.89)       | 2.37 (0.36)              | 8.68 (0.89)        | 9.27 (0.84)        | -1.47 (0.67)             | 3.84 (2.33, 5.34)                |
| ARC (x 10 <sup>9</sup> cells/L) | 217.5 (75.0)         | 77.7 (26.9)        | -135.8 (6.5)             | 216.2 (69.1)       | 220.0 (92.3)       | 27.8 (11.9)              | -163.6 (-189.9, -137.3)          |
| LDH (U/L)                       | 257.5 (97.6)         | 188.8 (79.2)       | -14.8 (42.7)             | 308.6 (284.8)      | 183.3 (28.8)       | -10.1 (71.0)             | -4.6 (-181.3, 172.0)             |
| FACIT-Fatigue                   | 32.2 (11.4)          | 42.5 (8.8)         | 9.2 (1.6)                | 31.6 (12.5)        | 34.7 (16.4)        | -2.7 (2.8)               | 11.9 (5.5, 18.3)                 |

Source: Section 2.5.1, pp 61-93 of the submission and the PEGASUS 16-week trial report

Abbreviations: ARC, absolute reticulocyte count; CI, confidence interval; LDH, lactate dehydrogenase; SD, standard deviation; SE, standard error

<sup>a</sup> Least squares mean analysed using an MMRM model including treatment, baseline value, visit and stratification factors (number of transfusions and platelet count at screening)

- 6.20 Treatment with pegcetacoplan was associated with a statistically significant improvement in Hb level compared to eculizumab in the absence of transfusions. The submission claimed the treatment difference of Hb 3.84 g/dL (in the absence of transfusions) is nearly twice the proposed MCID for change in Hb level (>2 g/dL) and is expected to translate into significant improvements in patients' energy and activity levels, as well as quality of life. In patients with PNH, the clinical importance of Hb level improvement as a single measure in the absence of clinical symptoms was uncertain.
- 6.21 For change in reticulocyte count, the upper bound of the 95% confidence interval of the adjusted treatment difference was less than the protocol-specified non-inferiority margin of 10 (x 10<sup>9</sup> cells/L), indicating that pegcetacoplan was noninferior to eculizumab in the absence of transfusions.
- 6.22 Pegcetacoplan did not meet the predefined non-inferiority criterion for change in LDH, as the upper bound of the 95% confidence interval of the adjusted treatment difference exceeded the protocol-specified non-inferiority margin of 20 U/L. The submission appeared to challenge the clinical importance of the pre-specified non-inferiority margin and changes in LDH level in the absence of clinical signs and symptoms. The ESC previously considered marked increases in LDH (as a marker of haemolysis) are not clinically significant in the absence of clinical symptoms such as fatigue and requirement for transfusion, and that transfusion avoidance, reduction in microthrombosis, macrothrombosis and stabilisation of haemoglobin levels are more clinically significant outcomes (para 6.45, ravulizumab PSD, July 2020 PBAC meeting).
- 6.23 Overall, the ESC considered the LDH results difficult to assess due to differences in baseline LDH levels between treatment arms. Patients randomised to pegcetacoplan had lower LDH levels compared to eculizumab, with a mean difference at baseline greater than the mean change from baseline to Week 16. Median baseline estimates also indicate greater variation in LDH levels in the eculizumab arm (median 212, range 122-1,598 U/L) compared to pegcetacoplan (median 247, range 119-584 U/L). There was substantial variation in LDH measures, particularly in the eculizumab arm, suggesting the mean values were skewed by outliers. The PSCR argued that given that the LDH levels in these patients had already been reduced by C5 inhibitor therapy, and

that there was an imbalance in the LDH levels between the groups, the magnitude of effect for change from baseline would be small, and the potential for change would favour the group with the higher baseline value. At week 16, the difference between the groups was -4.63U/L (95% -181 to 172.04) in favour of pegcetacoplan, with the upper bound of the 95% CI not being less than the prespecified non-inferiority margin of 20. The most prognostically relevant measure of LDH for survival was argued in the PSCR to therefore be measured in absolute values and normalisation, as opposed to change from baseline which does not guarantee reduced haemolysis risk. The PBAC agreed with the ESC that the LDH results were difficult to interpret due to differences in baseline LDH levels compared to eculizumab.

- 6.24 Non-inferiority for change in FACIT-Fatigue score was not assessed due to failure in the hierarchical testing (non-inferiority was not met for the LDH outcome). However, the submission claimed the treatment difference was over three times greater than the protocol-specified non-inferiority margin of -3, representing a clinically meaningful improvement in the FACIT-Fatigue score (Cella 2002).
- 6.25 The trial assessed quality of life based on the EORTC QLQ-C30 score. In the absence of transfusions, patients in the pegcetacoplan arm had numerical improvements in the global health status score and all functional scales compared to patients in the eculizumab arm. Pegcetacoplan was also associated with numerical improvements in the symptom scale score for fatigue. Changes in other symptom scores were difficult to interpret due to baseline differences between arms. The PBAC has previously questioned the appropriateness of EORTC QLQ-C30 scores used in trials of eculizumab and ravulizumab, noting the instrument is specifically used to assess the health-related quality of life of cancer patients (para 7.7, ravulizumab PSD, July 2020 PBAC meeting).
- 6.26 After completion of the 16-week randomised controlled period, patients in the pegcetacoplan group continued with pegcetacoplan monotherapy in the open-label period. Patients in the eculizumab arm received pegcetacoplan in addition to eculizumab during the second run-in period (Week 17 to 20) then pegcetacoplan monotherapy from Week 21 to 48. During the open-label period, efficacy endpoints were assessed as change from baseline as well as change from Week 17 (beginning of open-label period), using all available data (not censored for transfusion).
- 6.27 The results indicate a maintenance of treatment effect for the pegcetacoplan group and the eculizumab/pegcetacoplan group experienced similar increases in Hb level, reticulocyte count and FACIT-Fatigue scores upon switching to pegcetacoplan monotherapy. Results for LDH level were less stable, with fluctuations in mean estimates in both groups throughout the open-label period. Similar to the Week 16 primary analysis, there was substantial variation in LDH estimates due to outliers that may be skewing the mean estimates.
- 6.28 Transfusion avoidance was not a pre-specified outcome during the open-label period. During the evaluation, a post-hoc analysis of transfusion avoidance across the whole

study period was identified in the 48-week trial report. Across the whole study, the majority of patients who were randomised to the pegcetacoplan arm and continued on pegcetacoplan monotherapy achieved transfusion avoidance. The results were consistent but numerically smaller (73%) than the primary analysis based on 16 weeks of follow-up (85.4% of patients achieved transfusion avoidance). After switching to pegcetacoplan from eculizumab, the majority of patients achieved transfusion avoidance (72%), similar to the proportion in the pegcetacoplan group. The PBAC agree with the ESC that pegcetacoplan likely improved transfusion avoidance in the proposed PBS population, noting the magnitude of improvement varied over time.

- 6.29 The submission claimed that subgroup analyses were not relevant as the proposed PBS indication matched the key trial population. However, the submission acknowledged that approximately 30% of patients in the key trial were receiving higher doses of eculizumab than would be available in the Australian setting and the inclusion of these patients may bias the efficacy results in favour of eculizumab. To address this issue, the submission performed post-hoc subgroup analyses for key haematological measures (haemoglobin, reticulocyte count, LDH), transfusion avoidance and FACIT-Fatigue score in patients who were receiving standard dose eculizumab only. The ESC noted that the PBS listing of eculizumab would allow more frequent dosing of eculizumab if required, in line with its PI, and it considered that the higher dosing for eculizumab in the PEGASUS trial population is likely reasonably reflective of Australian practice going forward.
- 6.30 The results of the subgroup analyses were generally consistent with the primary analyses based on the censored for transfusion dataset, with pegcetacoplan associated with improvements in change from baseline to Week 16 in terms of Hb level, reticulocyte count and FACIT-Fatigue score and a higher proportion of patients with transfusion avoidance. LDH measures remained difficult to interpret due to substantial variation in the results (wide confidence intervals).
- 6.31 The submission claimed the results support similar efficacy with pegcetacoplan treatment in the subgroup of patients using the standard dose of eculizumab as observed in the whole trial population. The interpretation of these results was limited by the lack of subgroup characteristics and results for the complement group using higher doses of eculizumab. There were also more patients in the pegcetacoplan arm on higher doses of eculizumab compared with the eculizumab arm (36.6% vs 23.1% respectively), which resulted in fewer patients from the randomised arms informing the pegcetacoplan arm of this subgroup compared to the eculizumab arm.
- 6.32 The reasons for the use of varying doses and dosing frequencies of eculizumab in the trial population were unclear. The Australian product information suggests the dose regimen can be modified to every 12 days (rather than 14 days) in the presence of breakthrough haemolysis. However, there are potential health system differences impacting individual patient accessibility to higher doses and more frequent dosing of

- eculizumab. Differences in the distribution of patients on different dosing regimens may affect the level of haematological response to C5 inhibitors in the trial.
- 6.33 The submission claimed that pegcetacoplan is expected to reduce both intravascular and extravascular haemolysis and could in principle reduce the associated risk of kidney damage, but also that the development of life-threatening severe kidney disease in patients with PNH was rare. No data were provided in support of this claim.
- 6.34 The submission claimed based on expert opinion that pegcetacoplan is unlikely to provide any survival benefit compared to eculizumab or ravulizumab but assumed non-inferior survival outcomes based on short-term haematological outcomes. There are currently no studies assessing long-term outcomes with pegcetacoplan treatment including the prevention of disease-related complications and survival. The submission did not address potential differences in underlying risk in the broader PNH population compared to the requested subgroup who have suboptimal haematological response despite C5 inhibitor treatment. The ESC advised that long-term clinical data for pegcetacoplan was unlikely to be forthcoming for some time and thus the long-term relative benefit to C5 inhibitors was difficult to measure. The ESC also noted the PBAC recommendation for ravulizumab relied on non-inferior short-term outcomes comparative to eculizumab, which included transfusion avoidance, haemolysis (measured by LDH change), breakthrough haemolysis (BTH), quality of life and stabilised haemoglobin (para 6.8 and 7.10, ravulizumab PSD, July 2021 PBAC meeting).
- 6.35 The submission claimed that the historical leading cause of death in PNH was thrombosis, which is now well-managed with eculizumab treatment. The submission claimed that treated patients have comparable overall survival to the age-adjusted general population based on a comparison between eculizumab treated patients and a matched historical control in the UK (Kelly 2011). The evaluation considered this assumption was inadequately supported given the trial data indicated 23% of treated patients continued to experience serious or life-threatening events over the 48-week treatment period of the trial. The PBAC previously considered published survival data for eculizumab versus best supportive care (including the Kelly 2011 study) to be limited as the data were sparse, variable and largely dated (para 7.8, ravulizumab PSD, July 2021 PBAC meeting). The PBAC previously considered the results from the International PNH Registry supported a survival advantage for eculizumab over BSC and that, while the magnitude of that advantage remained uncertain, the claim of superior efficacy remained appropriate (para 7.8, ravulizumab PSD, July 2021 PBAC meeting).
- 6.36 The ESC noted the PSCR stated data from the Korean PNH Registry confirmed that patients with LDH  $\geq 1.5 \times \text{ULN}$  have a 4.8 fold higher mortality rate compared with age and gender matched members of the general population (Jang JH et al., 2016). The PSCR further claimed the PEGASUS study showed pegcetacoplan was able to normalise LDH in the absence of transfusions in 70.7% of patients vs 15.4% for

eculizumab at week 16. Using the data uncensored for transfusion, the majority of patients in both arms achieved LDH normalisation (pegcetacoplan 73.2%, eculizumab 59.0%; difference was not statistically significant).

### Comparative harms

6.37 A summary of key adverse events during the key trial including the run-in period (combination of the initial 4-week run-in period and second 4-week run-in period in eculizumab patients who switched to pegcetacoplan in the open-label period), 16-week randomised controlled period and 32-week open label pegcetacoplan period (pegcetacoplan monotherapy only) is presented in the table below.

**Table 6: Summary of key adverse events in the PEGASUS trial**

| Adverse event                                  | Run-in <sup>a</sup> | Randomised period |             | Open label  |
|--|---------------------|-------------------|-------------|-------------|
|  | PEG + ECU<br>N=80   | PEG<br>N=41       | ECU<br>N=39 | PEG<br>N=77 |
| Any AE, n (%)                                  | 71 (88.8)           | 36 (87.8)         | 36 (92.3)   | 71 (92.2)   |
| - Total events, n                              | 383                 | 272               | 162         | 696         |
| AE leading to treatment discontinuation, n (%) | 0                   | 3 (7.3)           | 0           | 9 (11.7)    |
| - Haemolysis                                   | 0                   | 3 (7.3)           | 0           | 2 (2.6)     |
| - Bone marrow failure                          | 0                   | 0                 | 0           | 1 (1.3)     |
| - Haemolytic anaemia                           | 0                   | 0                 | 0           | 1 (1.3)     |
| - Acute myeloid leukaemia                      | 0                   | 0                 | 0           | 1 (1.3)     |
| - Diffuse large B-cell lymphoma                | 0                   | 0                 | 0           | 1 (1.3)     |
| - Intestinal ischaemia                         | 0                   | 0                 | 0           | 1 (1.3)     |
| - COVID-19                                     | 0                   | 0                 | 0           | 1 (1.3)     |
| - Hypersensitivity pneumonia                   | 0                   | 0                 | 0           | 1 (1.3)     |
| AE leading to study discontinuation, n (%)     | 0                   | 1 (2.4)           | 0           | 9 (11.7)    |
| SAE, n (%)                                     | 4 (5.0)             | 7 (17.1)          | 5 (12.8)    | 18 (23.4)   |
| - Total events, n                              | 4                   | 8                 | 9           | 30          |
| SAE leading to study discontinuation, n (%)    | 0                   | 1 (2.4)           | 0           | 6 (7.8)     |
| Deaths, n (%)                                  | 0                   | 0                 | 0           | 1 (1.3)     |
| Grade 3+ severe adverse events                 | 4 (5.0)             | 8 (19.5)          | 4 (10.3)    | 18 (23.4)   |
| <b>Adverse events of special interest</b>      |                     |                   |             |             |
| Injection site reactions, n (%)                | 47 (58.8)           | 15 (36.6)         | 1 (2.6)     | 20 (26.0)   |
| Haemolytic disorders, n (%)                    | 1 (1.3)             | 5 (12.2)          | 14 (35.9)   | 18 (23.4)   |
| Hypersensitivity, n (%)                        | 15 (18.8)           | 5 (12.2)          | 2 (5.1)     | 14 (18.2)   |
| Infections, n (%)                              | 12 (15.0)           | 12 (29.3)         | 11 (28.2)   | 43 (55.8)   |
| Sepsis, n (%)                                  | 2 (2.5)             | 0                 | 0           | 3 (3.9)     |
| Thrombosis, n (%)                              | 0                   | 0                 | 0           | 2 (2.6)     |

Source: Table 38, p 177; Table 43, p 194; Table 50, p 220; Table 14.3.1.1.4, p1879 of the PEGASUS Week 48 trial report

Abbreviation: AE, adverse events; SAE, serious adverse events

<sup>a</sup> The run-in column includes adverse events during the first and second run-in periods

6.38 The most frequently reported adverse events during the first and second run-in periods (pegcetacoplan and eculizumab co-administration) were injection site erythema (41.3%), injection site pruritus (15.0%), diarrhoea (12.5%), headache (12.5%), injection site swelling (12.5%) and injection site reaction (10.0%). Four patients (5.0%) experienced serious adverse events of haemolysis, sepsis and nasopharyngitis.

- 6.39 Compared to eculizumab, pegcetacoplan was more frequently associated with injection site reactions, diarrhoea and hypersensitivity events. Seven patients (17.1%) in the pegcetacoplan arm experienced serious adverse events of haemolysis, infections (gastroenteritis, bacterial), dyspnoea, atrial fibrillation, pyrexia and facial paralysis. One patient experiencing haemolysis in the pegcetacoplan arm withdrew from the study. For the eculizumab group, 5 patients (12.8%) experienced serious adverse events of haemolysis, haemolytic anaemia, anaemia, abdominal pain, hyperthermia and hepatobiliary disorders. In terms of injection site reactions, the pre-PBAC response stated that such adverse events primarily occurred during the initiation phase and subsided over time. The pre-PBAC response argued that injection site reactions reported were mild or moderate in nature and none led to study discontinuation.
- 6.40 During the randomised period, 3 patients (7.3%) discontinued from the pegcetacoplan group because of haemolysis (2 were of moderate severity but deemed related to pegcetacoplan, 1 was a serious adverse event that was deemed unrelated to pegcetacoplan). No patients in the eculizumab arm discontinued prematurely.
- 6.41 Eighteen patients experienced a serious adverse event including blood and lymphatic system disorders (haemolysis, cytopenia, haemolytic anaemia, thrombocytopenia), infections and gastrointestinal disorders. One patient had an adverse event of COVID-19 that led to death.
- 6.42 The reporting of adverse events during the open label period was not stratified by the continue pegcetacoplan and crossover to pegcetacoplan groups, however, an analysis of exposure-adjusted incidence of adverse events suggests a higher frequency of adverse events in the crossover group compared to the continue group (175.9 vs 143.3 events per 100 person-years).
- 6.43 During the open label period, 9 patients (11.7%) discontinued because of haemolysis, bone marrow failure, haemolytic anaemia, acute myeloid leukaemia, diffuse large B-cell lymphoma, intestinal ischaemia, COVID-19 and hypersensitivity pneumonitis (6 patients experienced serious adverse events). Of the 9 patients who discontinued, 7 were in the crossover to pegcetacoplan group and 2 were in the continue pegcetacoplan group.
- 6.44 The submission claimed that the discontinuations from the pegcetacoplan arm because of haemolysis in the trial were not a safety concern, and that overall, there were fewer adverse events of haemolysis in the pegcetacoplan arm compared to the eculizumab arm. The submission claimed that patients discontinuing pegcetacoplan would return to currently approved PNH therapies such as eculizumab or ravulizumab when listed on the PBS.
- 6.45 The severity of breakthrough haemolysis events in the trial was based on a summary of individual patients who experienced breakthrough haemolysis during the randomised controlled period, identified in the supplementary appendix of the

PEGASUS trial publication (Hillmen 2021). There is currently no consensus in the published literature on the safety of pegcetacoplan in terms of haemolysis with some experts suggesting there is increased risk of severe breakthrough haemolysis while treated with pegcetacoplan that is mechanistically different to breakthrough haemolysis events while treated with C5 inhibitors.

- 6.46 The PEGASUS study authors responded to issues regarding the characterisation of breakthrough haemolysis in the trial, arguing against the suggestion that breakthrough haemolysis during receipt of pegcetacoplan is potentially life-threatening given that 3 of the 4 patients who had breakthrough haemolysis during pegcetacoplan therapy discontinued treatment, and none had major clinical consequences of long-lasting harm. These claims could not be validated during the evaluation.
- 6.47 In their response, the PEGASUS study authors recommended that patients switching from C5 inhibitors should be monitored closely for signs of breakthrough haemolysis. If breakthrough haemolysis occurs, the following options should be considered: immediate red cell transfusion, pegcetacoplan dose adjustment, short-term administration of eculizumab and identification and treatment of complement-amplifying conditions that may underlie the event. No data were provided in support of these recommendations. No documentation was available regarding the management of breakthrough haemolysis in the trial.
- 6.48 The ESC reflected on the original safety data from the eculizumab study, TRIUMPH (Hillmen et al, 2006<sup>1</sup>), noting that the most common adverse events reported in the eculizumab group were headache (44%), nasopharyngitis (23%), back pain (19%), and nausea (16%).

### **Benefits/harms**

- 6.49 A benefits/harms summary for the comparison of pegcetacoplan and eculizumab was not presented due to limitations with the available data. The clinical claims of superior improvements in haemoglobin level and non-inferior efficacy for PNH were based on short-term, 16-week outcomes of Hb level, transfusion avoidance, reticulocyte count and quality of life, with no survival data or long-term outcomes including the prevention of thromboembolism events. In terms of safety, there are no comparative data beyond the 16-week randomised period of the trial and a lack of consensus in the published literature regarding the safety of pegcetacoplan in terms of severity of breakthrough haemolysis events.

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<sup>1</sup> Hillmen P, Young NS, Schubert J, Brodsky RA, Socie G, Muus P, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med.* 2006 Sep 21;355(12):1233-43.

### **Clinical claim**

- 6.50 The submission described pegcetacoplan as superior in terms of improvements in haemoglobin level compared to eculizumab. The ESC considered the superiority claim in terms of improvements in haemoglobin level was reasonable and would likely lead to improvements in quality of life.
- 6.51 The submission described pegcetacoplan as at least non-inferior in terms of efficacy compared to eculizumab. The clinical claim in the submission was not specific but appeared to be based on numerical improvements and statistical non-inferiority in terms of short-term outcomes of transfusion avoidance, reticulocyte count and quality of life (associated with fatigue). The ESC noted that similar short-term outcome measures were used in the ravulizumab submissions (July 2021 and July 2022 PBAC meetings). The results for change in LDH level did not meet the protocol-specified non-inferiority margin. The clinical claim was uncertain in terms of long-term outcomes including life-threatening events such as thrombosis and survival.
- 6.52 The submission described pegcetacoplan as at least non-inferior in terms of safety compared to eculizumab. The ESC considered this claim was not well supported based on the safety data from PEGASUS, given patients who did not tolerate eculizumab were excluded from the trial. The ESC further noted that all patients enrolled in PEGASUS were already stable on eculizumab and hence would be less likely to experience adverse events. Referring back to original eculizumab study (TRIUMPH, Hillmen et al 2006) it would appear that the two are similar in toxicity profiles and the non-inferior safety claim was likely reasonable.
- 6.53 The PBAC considered that the evidence presented demonstrated a benefit in short-term haematological outcomes. In addition, the PBAC considered that while uncertain, the claim of non-inferior comparative effectiveness to the known benefits of eculizumab treatment in this population was reasonable.
- 6.54 The PBAC considered that the claim of non-inferior comparative safety was uncertain but reasonable.
- 6.55 The submission claimed that as ravulizumab is a pharmacological analogue of eculizumab and the PBAC has previously considered ravulizumab as non-inferior in efficacy and safety compared to eculizumab, then the comparative results from the PEGASUS trial would also be indicative of comparative efficacy and safety between pegcetacoplan and ravulizumab. The PBAC agreed with the ESC that this claim was reasonable.

### **Economic analysis**

- 6.56 The submission nominated the comparison of pegcetacoplan versus ravulizumab as the base case economic evaluation, claiming that ravulizumab is the most appropriate pricing comparator (based on a recent positive PBAC recommendation) and that the price of eculizumab may not be relevant as it was listed on the LSDP at the time of the

submission. The ESC noted both eculizumab and ravulizumab were recommended for PBS listing in July 2021, and the costs of both C5 inhibitors were considered relevant. The sponsor proposed that pegcetacoplan be listed [REDACTED] (see Table 7). The cost-effectiveness of these treatments in the subgroup who have suboptimal haematological response has not previously been considered by the PBAC.

**Table 7: Pegcetacoplan, eculizumab and ravulizumab price calculations**

|  | Value                 | Source/calculation  |
|--|-----------------------|---|
| <b>Estimated cost of eculizumab</b>    |                       |   |
| AEMP per vial                          | \$5,640.63            | Published AEMP for eculizumab for atypical haemolytic uraemic syndrome (aHUS) (PBS items 10182XX, 10183Y, 10190H, 10191J, 10192K, 10194M, 10521R, 10525Y).  |
| Vials per dose                         | 3                     | Number of vials required per 900 mg dose for the treatment of PNH.  |
| Cost per script (weighted DPMQ)        | \$[REDACTED]          | Calculated assuming 1 dose per script. Weighted DPMQ based on [REDACTED]% public hospital and [REDACTED]% private hospital split, representing the distribution of use for aHUS on the PBS.   |
| Dosing frequency                       | Every 14 days         | Assumption.   |
| Doses/scripts per year                 | 26.09                 | Calculated as 365.25 ÷ 14 days.   |
| Annual drug cost                       | \$[REDACTED]          | The annual drug cost was calculated as cost per script x scripts per year.  |
| <b>Estimated cost of pegcetacoplan</b> |                       |   |
| Dosing frequency                       | Every [REDACTED] days | Based on circumstances of use of pegcetacoplan during the 16-week randomised controlled period of the key trial (2/41, 4.9% received dose escalation to 1,080 mg every 3 days; remaining patients received 1,080 mg twice weekly). The weighted average frequency of dosing was every [REDACTED] days based on [REDACTED]% dosed every [REDACTED] days and [REDACTED]% dosed every [REDACTED] days. |
| Doses per year                         | [REDACTED]            | Calculated as 365.25 ÷ [REDACTED] days.   |
| Cost per dose                          | \$[REDACTED]          | Calculated as annual eculizumab drug cost divided by pegcetacoplan doses per year.  |
| Doses per script                       | [REDACTED]            | As per proposed PBS restriction.  |
| Cost per script (DPMQ)                 | \$[REDACTED]          | Calculated as cost per dose x doses per script.   |
| AEMP per vial                          | \$[REDACTED]          | The submission assumed a \$[REDACTED] fee and \$[REDACTED] mark-up would be applied to the Section 100 – HSD (Community Access) listing. The estimated AEMP for [REDACTED] vials was calculated as \$[REDACTED] - \$[REDACTED] = \$[REDACTED]. The estimated AEMP per vial was calculated as \$[REDACTED] ÷ [REDACTED] = \$[REDACTED].  |
| <b>Estimated cost of ravulizumab</b>   |                       |   |
| Doses per year                         | 6.52                  | Calculated based on recommended 8-weekly dosing interval (365.25 ÷ 56).   |
| Vials per dose                         | 11                    | Estimated maintenance dose of ravulizumab was 3,300 mg based on mean weight from the PEGASUS trial of 75.3 kg. Calculated using 300 mg vial size.   |
| Doses per script                       | 1                     | Assumption.   |
| Cost per script (weighted DPMQ)        | \$[REDACTED]          | Calculated using estimated annual cost of eculizumab (\$[REDACTED]) divided by the number of ravulizumab doses per year (6.52).   |
| AEMP per vial                          | \$[REDACTED]          | The AEMP for 11 vials was estimated by back calculating the public (\$[REDACTED]) and private hospital DPMQ (\$[REDACTED]) assuming a 90%/10% public/private split (same as eculizumab for aHUS on the PBS). The AEMP per vial was calculated as \$67,702.52 ÷ 11.  |

Source: Table 3-10, p 140; Table 3-11, p 141 of the submission

Abbreviations: AEMP, ex-manufacturer price; DPMQ, dispensed price maximum quantity

6.57 The evaluation considered there were multiple concerns with the approach used to estimate the AEMP of pegcetacoplan in the economic model of the submission. Key

issues with the estimated annual drug costs of eculizumab and ravulizumab include the assumption that each script provides 1 dose (i.e. 2-week script coverage for eculizumab and 8-week script coverage for ravulizumab) and the calculation of prices that were based on dispensed prices including fees and mark-ups. The estimated trial-based dosing frequency of pegcetacoplan is likely to result in underestimated pegcetacoplan drug costs with the open-label period data suggesting more patients received escalated doses over time. The PBAC noted the estimated maintenance dose of ravulizumab was 3,300 mg administered 6.52 times per year (total dose 21,524 mg). The PBAC recalled that in its July 2021 consideration of ravulizumab dosing was based on a maintenance dose of 3,288 mg administered 6.5 times per year (total dose 21,375 mg) (paragraph 6.64, Table 9, ravulizumab PSD, July 2021 PBAC meeting).

- 6.58 During the evaluation, cost-effectiveness analyses of pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab were presented separately using results from the model provided in the submission (see relevant sub-sections below).

***Pegcetacoplan versus eculizumab***

- 6.59 The submission presented a cost-utility analysis of pegcetacoplan versus eculizumab for the treatment of adult patients with PNH who have a Hb level <10.5 g/dL despite receiving a stable dose of C5 inhibitor treatment for at least 3 months. The economic evaluation was a cost-utility analysis based on data from the PEGASUS trial and other modelled variables.

**Table 8: Key components of the economic evaluation**

| Component                        | Summary   |
|----------------------------------|---|
| Treatments                       | Pegcetacoplan versus eculizumab   |
| Time horizon                     | 51.2 years in the model base case (to age 100 years) versus 48 weeks in the PEGASUS trial (16 weeks randomised controlled period and 32 weeks open label pegcetacoplan period)  |
| Outcomes                         | Life-years and quality-adjusted life-years (QALYs)  |
| Methods used to generate results | Markov cohort model   |
| Health states                    | No transfusion and Hb<10.5, no transfusion and Hb≥10.5, transfusion required, dead  |
| Cycle length                     | 4 weeks, half-cycle corrections   |
| Transition probabilities         | <p>Transition probabilities to the alive health states were derived using a re-analysis of patient-level data from the PEGASUS trial classifying patients into the defined health states by transfusion status and Hb level. The re-analysis was used to inform a multinomial regression model that predicted the current health state based on the prior health state (last 4 weeks), treatment, visit category and age. Two sets of transition probabilities were derived for each treatment arm, used in the first 4-week cycle and all subsequent cycles in the model.</p> <p>Treatment discontinuations were based on the study discontinuation rate in the trial and assumptions, applied as a one-off probability at 16 weeks in the model to the pegcetacoplan arm only. Patients who discontinued were assumed to switch to ravulizumab treatment for the remainder of the modelled duration. Patients switching to ravulizumab were assumed to remain in their prior health state or die. Patients treated with eculizumab and ravulizumab (in those discontinuing from pegcetacoplan) were assumed to be 100% persistent to therapy.</p> <p>The probability of death was based on age- and gender-adjusted Australian general population mortality.</p> <p>94% of QALYs and 94% of cost savings are accrued in the extrapolated period</p> |
| Costs                            | Drug acquisition costs for pegcetacoplan, eculizumab and ravulizumab estimated assuming [REDACTED] based on the published price of eculizumab for atypical haemolytic uraemic syndrome on the PBS as a proxy. One-off administration costs included for pegcetacoplan and ongoing administration costs for eculizumab and ravulizumab. Vaccine costs (initial and boosters) included for both treatment arms. Disease management costs based on blood transfusions, iron overload treatment and monitoring costs. Adverse event costs based on serious adverse events in the trial.   |
| Health related quality of life   | Trial-based EORTC QLQ-C30 scores from the PEGASUS trial were mapped to EQ-5D-3L utility estimates using the Longworth 2014 mapping algorithm. Using mapped values, a Tobit regression model was used to predict the following health state utilities: no transfusion and Hb<10.5: 0.7553, no transfusion and Hb≥10.5: 0.8192 and transfusion required: 0.7202. The iron chelation therapy disutility of -0.0092 per cycle was derived from a published cost-effectiveness analysis. An age-specific utility adjustment was applied based on age-related decline in general population utility estimates.  |
| Discount rate                    | 5% for costs and outcomes, applied annually   |
| Software package                 | Excel   |

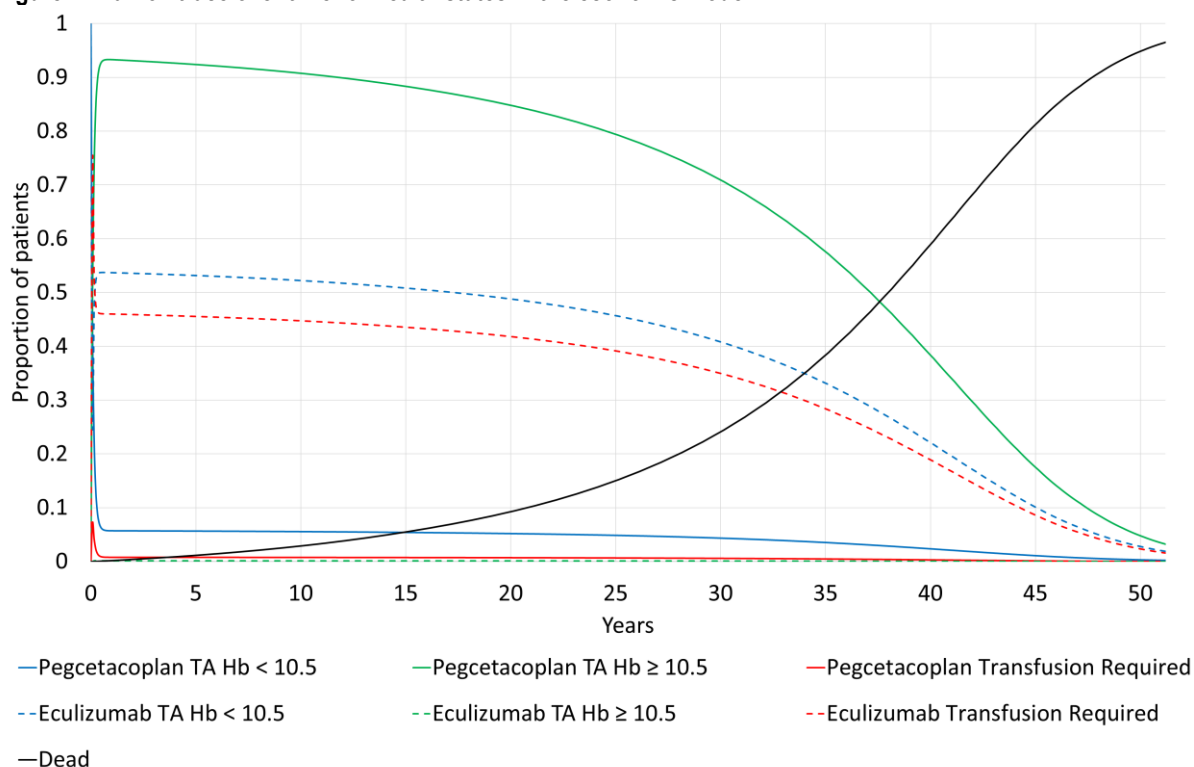
Source: Table 3-1, p 125; and Sections 3.4 to 3.6, pp 130-148 of the submission

Abbreviations: Hb, haemoglobin

- 6.60 Overall, there was a lack of transparency relating to various key inputs in the model that hindered the evaluation of the economic analysis, including the re-analysis of patient-level data used to derive the transition probabilities, assumptions regarding patient flow during the trial, limited documentation regarding the estimation of utility values, source data informing costs associated with blood transfusion and disease monitoring and source data used to calculate adverse event rates.
- 6.61 The economic evaluation was based on a Markov cohort state transition model using a four-week cycle length. The model consisted of four mutually exclusive health states:

- No transfusion and Hb<10.5: patients who did not require a red blood cell transfusion in the 4 weeks prior and had a Hb level less than 10.5 g/dL.
  - No transfusion and Hb≥10.5: patients who did not require a red blood cell transfusion in the 4 weeks prior and had a Hb level of 10.5 g/dL or greater.
  - Transfusion required: patients who required a red blood cell transfusion in the 4 weeks prior.
  - Dead: absorbing health state.
- 6.62 All patients begin in the baseline health state of no transfusion and Hb<10.5. In the first cycle, patients can remain in the baseline state, transition to the no transfusion and Hb≥10.5 state, transition to the transfusion required state or die. In subsequent cycles, patients can remain in their state or transition to any of the states in the model. Death is an absorbing state.
- 6.63 The submission stated that a Hb level of less than 10.5 g/dL was chosen to be consistent with the inclusion criteria of the PEGASUS trial. The use of Hb levels to represent differences in costs and outcomes in patients who are not receiving transfusions was inadequately discussed in the submission. It may not be appropriate to assume differences due to Hb levels alone in the absence of clinical symptoms.
- 6.64 Transfusion status was determined based on whether patients required a transfusion in the previous 4 weeks. The 4-week cycle length appears short given transfusion avoidance was measured over a 16-week period in the key trial of pegcetacoplan and over a 26-week period in Trial 302 of ravulizumab versus eculizumab. The LSDP eligibility criteria for eculizumab includes having at least 4 transfusions over a 12-month period. The clinical importance of modelled outcomes based on transfusion status and/or Hb level over a 4-week duration was uncertain.
- 6.65 Overall, the model structure limited the attribution of costs and benefits to health states based on transfusion status and Hb levels alone, without adequately accounting for other disease-related symptoms or need for medical interventions apart from treatment of iron overload. The exclusion of haemolytic events in the base case of the economic model was inadequately justified given the occurrence of these events during the trial, some of which were serious or life-threatening. All treatment discontinuations of pegcetacoplan in the randomised controlled period of the trial were due to breakthrough haemolysis. The pre-PBAC response argued that not all disease-related complications or medical interventions were modelled because no differences are expected between treatments in this regard.
- 6.66 The use of health states defined by transfusion status and Hb levels assumed equivalence in the treatment efficacy of pegcetacoplan versus eculizumab for the prevention of long-term outcomes including life-threatening events such as thrombosis and survival. No data were provided in support of this assumption.
- 6.67 The figure below is a Markov trace over time for the health states of no transfusion and Hb<10.5, no transfusion and Hb≥10.5, transfusion required and dead.

Figure 1: Markov trace over time for health states in the economic model



Source: constructed during the evaluation using the 'Pegcetacoplan\_CEA\_AUS\_FINAL' Excel workbook of the submission  
 Abbreviation: TA, transfusion avoidance

- 6.68 The Markov trace shows rapid transitions in the first 2 model cycles (described in more detail below). After this timepoint, the proportion of patients remaining in each alive health state appeared stable over time except for a general decline due to death which occurred equally between health states.
- 6.69 The trace shows the majority of patients in the pegcetacoplan arm remain in the no transfusion and  $Hb \geq 10.5$  health state for most of the modelled duration, with a relatively small proportion of patients in the no transfusion and  $Hb < 10.5$  health state and very few patients in the transfusion required health state. The ESC considered this was implausible. The pre-PBAC response argued that data from the 48-week open label period showed that patients in the pegcetacoplan arm have significant and sustained improvement in their Hb level. In addition, the pre-PBAC response stated that throughout the 48 week open label period 73% of patients continuing on pegcetacoplan monotherapy and 72% of patients in the cross-over group from eculizumab to pegcetacoplan remain transfusion independent. As such, the pre-PBAC response argued that it was clinically plausible that patients treated with pegcetacoplan would remain in the optimal health state. The PBAC considered that while pegcetacoplan likely improved transfusion avoidance, the magnitude of improvement varied over time (see paragraph 6.28). The PBAC agreed with the ESC that the health state assumptions made for pegcetacoplan were implausible.

- 6.70 In the eculizumab arm, more patients remained in the no transfusion and Hb<10.5 health state with marginally fewer patients in the transfusion required health state and almost no patients in the no transfusion and Hb≥10.5 health state.
- 6.71 The difference in the distribution of patients across the alive health states between arms was the driver of cost savings and improved quality of life associated with pegcetacoplan in the model. There was no difference in survival between the pegcetacoplan and eculizumab arms.
- 6.72 Based on the Markov trace, approximately 50% of patients with PNH treated with pegcetacoplan, eculizumab and ravulizumab were still alive at age 86.8 years (modelled duration 38 years). This was based on the assumption that the subgroup of PNH patients who have suboptimal haematological response to C5 inhibitors but continue with treatment would have the same mortality as the general population. This assumption did not appear clinically plausible and was inconsistent with data suggesting 23% of patients experienced serious and life-threatening events during the whole study period.
- 6.73 Key drivers of the economic model are summarised in the table below.

**Table 9: Key drivers of the model**

| Description                           | Method/Value   | Impact                      |
|---------------------------------------|--|-----------------------------|
| Model structure                       | The model structure was limited to health states based on transfusion status and Hb levels alone which favoured pegcetacoplan due to the claimed benefits and reduced costs associated with the defined health states.   | High, favours pegcetacoplan |
| Health state transition probabilities | The transition probabilities were estimated using patient-level data from the PEGASUS trial by first classifying patients into the pre-defined health states of the model (no transfusion and Hb<10.5, no transfusion and Hb≥10.5 and transfusion required) depending on their medical characterisation on the planned visits during the PEGASUS study treatment period. This re-analysis of transfusions and Hb levels using individual patient data could not be evaluated or reconciled with key trial outcomes in the clinical section as the data were not presented in the submission. The analysis was requested from the sponsor during the evaluation, however, the sponsor responded that they were unable to provide the patient-level data used for the analysis as it was against company policy to release such information. The implementation of these inputs was the primary driver of modelled cost savings and incremental benefit associated with pegcetacoplan, due to the difference in time spent in each health state between treatment arms.  | High, favours pegcetacoplan |
| Treatment discontinuations            | The submission made a number of claims pertaining to patient flow during the trial (treatment discontinuations, study discontinuations and continuation to the open label period) and management of breakthrough haemolysis that could not be validated during the evaluation as the data were not provided in the submission. The submission made further assumptions to derive the treatment discontinuation rates and consequences following discontinuation that were inadequately supported. The assumed consequences following discontinuation favoured pegcetacoplan as patients switching to ravulizumab have a fixed health status in terms of Hb level and transfusion requirements over the remaining modelled duration.  | High, favours pegcetacoplan |
| Background mortality                  | The submission calculated age- and gender-specific mortality rates in the Australian population based on the Australian Bureau of Statistics 2017-2019 life tables. This was used as background mortality in all health states, assuming that patients with PNH who are treated with pegcetacoplan, eculizumab and ravulizumab have the same mortality rate as the general population. No data are available to support non-inferior survival between these treatments. The assumption that treated patients achieve general population mortality was inadequately supported given 23% of treated patients continued to experience serious or life-threatening events over the 48-week trial.  | High, favours pegcetacoplan |
| Iron overload treatment               | The proportion of patients requiring iron overload treatment in the model was estimated using prior medication use of deferasirox (19/80, 23.75%) or desferrioxamine (3/80, 3.75%) within 12 weeks of the screening visit of the PEGASUS trial. The use of historical estimates was inadequately justified given the availability of utilisation data for iron chelation therapies during the trial. The submission inappropriately used the same fixed utilisation estimates of iron chelation therapies to represent the proportion of patients requiring treatment for iron overload in each treatment arm regardless of changes in the proportion of patients in each health state. The submission inappropriately assumed that patients receiving pegcetacoplan do not require chelation therapy for iron overload as they have sufficient haemoglobin levels that allow for therapeutic venesection (removal of iron by removing blood) whereas patients receiving eculizumab would be treated with iron chelation therapy for iron overload. This assumption led to differences in costs and quality of life that favoured pegcetacoplan. | High, favours pegcetacoplan |

| Description  | Method/Value  | Impact                      |
|--|---|-----------------------------|
| Health state utility values  | Health state utilities were derived using EORTC QLQ-C30 scores in the PEGASUS study, mapped to EQ-5D-3L utility values using a multinomial regression model and UK tariffs based on cancer patients (Longworth 2014). The PBAC has previously questioned the appropriateness of EORTC QLQ-C30 scores used in trials of eculizumab and ravulizumab, noting the instrument is specifically used to assess the health-related quality of life of cancer patients (para 7.7, ravulizumab PSD, July 2020 PBAC meeting). The predictability of the mapping algorithm when used for a bleeding disorder (unrelated to cancer) is unclear. The reliability of the Tobit regression model used to estimate the health state utilities was uncertain due to limited documentation in the submission. The application of different utility values to the no transfusion health states assumed a difference in quality of life could be attributed to Hb level alone, which was inadequately justified in the submission.   | High, favours pegcetacoplan |
| Complement inhibitor treatment costs   | Drug acquisition costs for pegcetacoplan, eculizumab and ravulizumab were calculated assuming [redacted] [redacted] on an annual basis (maintenance year only) should eculizumab and ravulizumab be listed on the PBS. The submission used the published eculizumab price for atypical haemolytic uraemic syndrome (aHUS) on the PBS as a proxy for the published price of eculizumab for PNH on the PBS. The published PBS price of eculizumab for aHUS is unlikely to represent the PBS price of eculizumab for PNH. There were multiple concerns with the approach used in the submission including assumptions surrounding PBS script coverage for eculizumab and ravulizumab, the use of DPMQ rather than AEMP in the pricing calculations, assumed circumstances of use of pegcetacoplan (i.e. proportion with dose escalation) and assumption of equivalent cost between eculizumab and ravulizumab. Overall, the submission’s approach was reliant on the assumption that the effective prices of eculizumab and ravulizumab represent a cost-effective price for pegcetacoplan. The relevance of both eculizumab and ravulizumab prices was uncertain as the cost-effectiveness of these treatments in the subgroup who have suboptimal haematological response has not been considered. | Unclear                     |
| Drug administration costs, blood transfusion costs, disease monitoring costs | The estimation of these costs was reliant on data sources and assumptions that were inadequately justified in the submission, which resulted in substantial cost offsets. The cumulative impact of these inputs on the economic analysis is likely to be substantial.   | High, favours pegcetacoplan |

Source: constructed during the evaluation

6.74 The results of the modelled economic evaluation are presented in the table below.

**Table 10: Results of the economic evaluation of pegcetacoplan versus eculizumab**

|   | Pegcetacoplan | Eculizumab | Increment       |
|---|---------------|------------|-----------------|
| Costs (\$)                              | [redacted]    | [redacted] | -               |
| QALYS                                   | 13.10         | 11.86      | 1.24            |
| <b>Incremental cost per QALY gained</b> |               |            | <b>Dominant</b> |

Source: constructed during the evaluation using the 'Pegcetacoplan\_CEA\_AUS\_FINAL' Excel workbook of the submission

Abbreviation: QALY, quality adjusted life year

6.75 The claimed benefits and reduced cost associated with pegcetacoplan versus eculizumab when assuming [redacted] [redacted] resulted in a 'dominant' base case. The results were consistently dominant due to the claim of superior quality of life outcomes, assumed equivalence in terms of survival outcomes and claim of reduced costs associated with administration, blood transfusions, disease monitoring and iron overload.

6.76 These results were not considered reliable due to the following concerns with the modelled cost savings and outcomes:

- The appropriateness of the model structure and validity of predicted outcomes was uncertain. Modelled outcomes were limited to differences based on transfusion status and Hb level alone, without adequately accounting for other disease-related complications.
- The assumption of non-inferior efficacy of pegcetacoplan versus eculizumab for the prevention of long-term outcomes including life-threatening events such as thrombosis and survival was uncertain.
- The differences in costs and outcomes were primarily driven by time spent in the optimal health state, using transition probabilities that could not be validated during the evaluation as the source analysis was not provided.
- Modelled cost savings associated with pegcetacoplan were substantial and largely based on cost inputs that were inadequately justified including drug administration costs, blood transfusion costs, disease monitoring costs and iron overload treatment costs.
- Modelled improvements in quality of life were uncertain as they were based on the assumption that any differences could be attributed to transfusion status and Hb levels alone. This approach inappropriately assumed no other factors had an impact on quality of life including the occurrence of serious or life-threatening events and treatment modality (e.g. higher frequency of administrations associated with pegcetacoplan).

6.77 Results of sensitivity analyses showed the results remained dominant despite changes in any parameter, which is expected given greater time spent in the optimal health state (no transfusion and  $Hb \geq 10.5$ ) and assumed equivalence in terms of survival outcomes leading to reduced costs and improved quality of life with pegcetacoplan treatment.

6.78 The submission acknowledged that the proportion of patients receiving pegcetacoplan dose escalations (4.9% during the randomised period used in the base case versus 19.5% during the open label period) had the largest impact on the difference in costs between arms. However, the submission claimed that the use of trial-based estimates may bias against pegcetacoplan as dose escalations may only be temporary in practice while the sensitivity analysis assumed ongoing escalated dosing frequency. No data were provided in support of this claim. Neither the trial protocol nor the draft product information indicated that dose frequency escalations would be temporary.

#### ***Pegcetacoplan versus ravulizumab***

6.79 The model structure and inputs for the pegcetacoplan versus ravulizumab comparison were largely the same as for the pegcetacoplan versus eculizumab comparison, except for a relatively small difference in administration costs and adverse events costs.

6.80 The submission's approach assumed non-inferiority between ravulizumab and eculizumab within the target population. The submission claimed that as ravulizumab

is a pharmacological analogue of eculizumab and the PBAC has previously considered ravulizumab as non-inferior in efficacy and safety compared to eculizumab, then the comparative results from the PEGASUS trial would also be indicative of comparative efficacy and safety between pegcetacoplan and ravulizumab. While the assumption of non-inferiority between ravulizumab and eculizumab was reasonable, the magnitude of benefit in the subgroup with suboptimal haematological response was unknown.

- 6.81 The estimated costs of ravulizumab treatment were the same as applied in the pegcetacoplan versus eculizumab model, to patients who discontinued pegcetacoplan and switched to ravulizumab. There were concerns with the basis of ravulizumab’s price (assumption of equivalence to eculizumab’s price), the inclusion of fees and mark-ups in the **||** calculations, and potential applicability issues with trial-based weights used to determine the dose of ravulizumab.
- 6.82 The estimated administration cost for ravulizumab was inappropriate as it was based on an assumed infusion duration of 2 hours. The assumption was based on outdated information, with an updated product information (October 2021 revision) recommending infusion durations of 40 minutes for 3,300 mg. The Manual of Resource Items v5.0 recommends the use of a standard MBS consultation item if there is no specific MBS item for the administration of the proposed drug.
- 6.83 Adverse event costs were the same as applied to patients who discontinued pegcetacoplan and switched to ravulizumab in the comparison against eculizumab. These costs should not be considered reliable due to the inadequately justified selection of adverse events, poor documentation surrounding the derivation of adverse event rates and inappropriate costing approach used in the submission.
- 6.84 The results of the modelled economic evaluation are presented in the table below.

**Table 11: Results of the economic evaluation of pegcetacoplan versus ravulizumab**

| Component                           | Pegcetacoplan | Ravulizumab | Increment       |
|-------------------------------------|---------------|-------------|-----------------|
| Costs (\$)                          |               |             | <b>↓</b>        |
| QALYs                               | 13.10         | 11.86       | 1.24            |
| <b>Incremental cost/QALY gained</b> |               |             | <b>Dominant</b> |

Source: Table 3-25, p 154 of the submission

Abbreviation: QALY, quality-adjusted life year

- 6.85 Results were consistent with the comparison versus eculizumab, although the cost savings were smaller due to differences in administration costs and adverse event costs.

### **Drug cost/patient/year**

- 6.86 The estimated drug costs per patient per year were calculated assuming **■ ■** between pegcetacoplan, eculizumab and ravulizumab. The submission acknowledged that the PBS listing status and prices of eculizumab and ravulizumab for PNH were unknown at the time of submission. Therefore, the submission used the published eculizumab price for aHUS on the PBS as a proxy for the published price of eculizumab

for PNH on the PBS. The same costs were applied in the economic analysis and financial estimates.

- 6.87 The estimated drug cost per patient per year for pegcetacoplan, based on a proposed DPMQ of \$| for | x 1,080 mg vials, was \$| in a maintenance year (| scripts).
- 6.88 The estimated drug cost per patient per year for eculizumab, based on an estimated weighted DPMQ of \$| for | x 300 mg vials, was \$| in a maintenance year (26.09 scripts).
- 6.89 The estimated drug cost per patient per year for ravulizumab, based on an estimated weighted DPMQ of \$| for | x 300 mg vials, was \$| in a maintenance year (6.52 scripts).
- 6.90 The submission inappropriately assumed that the drug acquisition costs of ravulizumab would be equivalent to eculizumab. The cost-minimisation analysis which formed the basis of PBAC’s positive recommendation for ravulizumab included cost offsets associated with differences in administration frequencies between ravulizumab and eculizumab (para 6.67, ravulizumab PSD, July 2021 PBAC meeting). Thus, the drug cost of ravulizumab is likely to be higher than the estimated cost of eculizumab.

### **Estimated PBS usage & financial implications**

- 6.91 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of pegcetacoplan, for the treatment of adult patients with PNH who have inadequate clinical response to C5 inhibitor treatment (haemoglobin level <10.5 g/dL after ≥3 months of stable treatment).
- 6.92 Key inputs used to derive the financial estimates are presented in the table below.

**Table 12: Key inputs for financial estimates**

| Parameter  | Value applied and source   | Comment  |
|--|--|--|
| <b>Eligible population and utilisation estimates</b> |  |  |
| PNH prevalence                                       | 1.66/100,000/year. Based on an incidence and prevalence study in Yorkshire, England on patients diagnosed with PNH from 1991-2006 (Hill 2006, abstract only) and expert opinion.                   | The results from the Hill study should be interpreted with caution due to limited detail available from the abstract. The results may not be applicable to the current Australian setting as the data were relatively old and collected prior to the established use of eculizumab for the treatment of PNH. |
| PNH incidence  | 0.13/100,000/year. Based on the Hill 2006 study (described above) and expert opinion.  | The prevalence estimate used in the submission was higher than the estimate reported in the Hill study of 1.59/100,000/year and could not be validated during the evaluation.  |
| Proportion treated with a C5 inhibitor               | 33.3%. Based on the proportion of patients with classic PNH (702/2356, 30% reported with haemolytic PNH) in the Socie 2016 study of patients in the International PNH registry and expert opinion. | The expert opinion was not provided in the submission. It was unclear whether the distribution of subcategories of PNH from the registry were applicable to the Australian setting, and whether all patients with classic PNH would qualify for treatment with a C5 inhibitor.                               |

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| Parameter  | Value applied and source  | Comment   |
|--|---|---|
| Patients with Hb<10.5 g/dL, no transfusion       | 43.9%. Based on an exploratory study of persistent extravascular haemolysis in PNH patients treated with eculizumab (Risitano 2009). Proportion based on 18/41 patients with major haematological response (transfusion independence and Hb levels of ≥8 g/dL)              | The determination of the eligible population was based on suboptimal haematological response (defined as Hb level less than 10.5 g/dL as per the proposed restrictions). The proportion of patients meeting the nominated Hb threshold was based on a relatively old exploratory analysis of haematological response to eculizumab. The applicability of these estimates to the PBS population was uncertain as it was based on a mix of continuing and newly treated eculizumab patients from the eculizumab extension trial which may not represent patients who have received treatment for much longer durations. |
| Patients with Hb<10.5 g/dL, transfusion required | 19.5%. Based on the Risitano study (described above). Proportion based on 8/41 patients with partial/minor response (patients with ≥50% or no reduction in transfusions).   |   |
| Uptake rate in patients with no transfusion      | █-█%. Assumption based on the expectation of a modest uptake due to transfusion independence and a lower perceived clinical need.   | The definition of transfusion dependence/ independence was not clear in the submission but is likely subjective in practice based on frequency of transfusions as well as number of units of blood transfused. No clear definition of clinical need was provided in the submission. Overall, the uptake of pegcetacoplan in the Australian setting is uncertain.  |
| Uptake rate in patients requiring transfusion    | █-█%. Assumption based on the expectation of higher uptake due to greater clinical need.  |   |
| Pegcetacoplan treatment persistence              | 97.56%. Based on the pegcetacoplan discontinuation rate of 2.44% applied in the economic model of the submission. Patients were assumed to discontinue treatment after receiving the initial script (4 weeks) only.   | The discontinuation rate was inconsistent with trial data indicating 3 patients (7.3%) had stopped pegcetacoplan due to breakthrough haemolysis. The assumption of 100% persistence after 4 weeks of treatment was inappropriate as it did not account for demonstration of clinical improvement or stabilisation of disease that were proposed as continuing treatment criteria in the restriction.  |
| Adherence to complement inhibitors               | 100%. Based on treatment compliance to pegcetacoplan in the key trial.  | Trial-based treatment adherence to pegcetacoplan may not be applicable to the real-world setting due to the complex method of administration, high rate of injection-site reactions, longer term tolerability concerns with frequent administrations and additional safety concerns that are likely to arise in less supervised, home-based settings. Treatment adherence to eculizumab was not captured during the trial.  |
| Pegcetacoplan scripts/patient/year               | Initial script: █; continuing scripts: █. Weighted average based on 95.1% of patients receiving standard dose pegcetacoplan (twice weekly) and 4.9% of patients receiving a dose escalation (every 3 days), based on the 16-week randomised controlled period of the trial. | The use of 16-week data to inform the proportion of patients with dose escalations is likely to result in underestimated use of pegcetacoplan given more patients (19.5%) received dose escalations during the 32-week open label period. The submission did not justify the assumption of increased dosing frequency while patients are in their run-in period (covered by the initial script), which is inconsistent with the trial and recommendation in the draft product information.  |
| <b>Key cost offsets to the PBS/RPBS</b>          |   |   |
| Ravulizumab substitution rate                    | 100%. Assumption.   | This assumption may not be appropriate as the eligible population could include patients who were failing C5 inhibitor treatment and may not qualify for ongoing treatment with ravulizumab on the PBS.   |
| Ravulizumab compliance rate                      | 100%. Assumption.   | No data were provided in support of this assumption.  |

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| Parameter   | Value applied and source   | Comment   |
|---|--|---|
| Ravulizumab scripts/patient/year  | 6.52. Assumption that each script provides 8 weeks of treatment.   | The script coverage was assumed as the PBS listing status of ravulizumab was unknown at the time of submission.   |
| Proportion of patients treated with iron chelation therapies while on ravulizumab | 23.75% on deferasirox, 3.75% on desferrioxamine. The proportion of patients treated with iron chelation therapies within 12 weeks of the screening visit of the PEGASUS trial. The submission assumed only patients treated with ravulizumab would receive iron chelation therapies for iron overload. | The proportion of patients treated with iron chelation therapies was inadequately justified as it was based on historical use rather than concomitant use during the trial. The assumption that patients on pegcetacoplan would only receive therapeutic venesection as iron overload treatment was inconsistent with trial data indicating patients treated with pegcetacoplan were receiving iron chelation therapy (21.9% during the randomised period and 14.3% during the open label extension period). The PBAC agreed with the ESC that there was no reason to think that the pegcetacoplan population will have no requirement for iron overload treatment. |
| Deferasirox scripts/patient/year  | 10.15. Based on a mean daily dose of 1,580.25 mg used in the economic model. The submission used a rounded estimate of 1,800 mg daily (5 tablets) with each script providing 180 tablets lasting 36 days. Scripts/year calculated as 365.25/36 days.   | The estimated number of scripts was uncertain as it was based on an assumed dose regimen (21 mg/kg/day, calculated as the average of a starting dose of 14 mg/kg/day and a maximum dose of 28 mg/kg/day reported in the deferasirox July 2018 PSD) and mean weight in the PEGASUS trial (75.3 kg). The use of rounded estimates (rounded up) may overestimate the average utilisation in the population.  |
| Desferrioxamine scripts/patient/year  | 5.48. Based on a mean daily dose of 2,633.75 mg used in the economic model. The submission used a rounded estimate of 3,000 mg daily (6 vials, no sharing) with each script providing 400 vials lasting 66.7 days. Scripts/year calculated as 365.25/66.7 days.  | The estimated number of scripts was uncertain as it was based on an assumed dose regimen (35 mg/kg/day) and mean weight in the PEGASUS trial (75.3 kg). The use of rounded up estimates may overestimate the average utilisation in the population.   |

Source: Table 4-1, p 160; Sections 4.1 to 4.5, pp 160-185 of the submission

- 6.93 The submission stated that utilisation data for therapies on the LSDP are not publicly available, therefore it was not possible to estimate the financial impact of pegcetacoplan using a market share approach. The submission claimed there is a paucity of published evidence pertaining to the epidemiology of PNH in Australia due to the rarity of the disease. The submission attempted to elicit Australian-specific data via market research and interviews with key opinion leaders which included two former PBAC members with LSDP expertise, a former MSAC member with PBAC expertise and four haematologists with experience in treating patients with PNH. Documentation of the interviews was not provided in the submission.
- 6.94 The ravulizumab July 2021 resubmission provided market share estimates for eculizumab on the LSDP using the sponsor's proprietary data, with an adjustment for additional known patients in the sponsor's clinical trials and competitor clinical trials (Table 17, ravulizumab PSD, July 2021 PBAC meeting).
- 6.95 The prevalent pool of patients was only used to estimate the number of eligible patients who would switch to pegcetacoplan in the first year. The estimated eligible population in subsequent years was calculated using incidence estimates. No

justification was provided for the assumption that all eligible patients would switch to pegcetacoplan in the first year of availability only. Over time, some patients may become eligible to switch to pegcetacoplan due to fluctuations in Hb levels. This approach is likely to underestimate the size of the eligible population over time.

6.96 The submission requested grandfathering but assumed these patients are already included within the prevalent population estimates, therefore separate estimates were not included for grandfathered patients.

6.97 The table below presents the estimated financial impact of listing pegcetacoplan

**Table 13: Estimated use and financial implications**

|  | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--|--------|--------|--------|--------|--------|--------|
| <b>Estimated extent of use</b>                             |        |        |        |        |        |        |
| Total treated patients                                     | 1      | 1      | 1      | 1      | 1      | 1      |
| Total initiating scripts                                   | 1      | 1      | 1      | 1      | 1      | 1      |
| Total continuing scripts                                   | 1      | 1      | 1      | 1      | 2      | 2      |
| Total PBS scripts  | 1      | 1      | 1      | 1      | 2      | 2      |
| <b>Estimated financial implications of pegcetacoplan</b>   |        |        |        |        |        |        |
| Cost to PBS less co-pay (\$)                               | 3      | 3      | 3      | 3      | 3      | 3      |
| <b>Change in utilisation of other medicines</b>            |        |        |        |        |        |        |
| PBS cost of displaced ravulizumab less co-pay              | 3      | 3      | 3      | 3      | 3      | 3      |
| PBS cost of displaced iron chelation therapies less co-pay | 4      | 4      | 4      | 4      | 4      | 4      |
| <b>Net financial implications</b>                          |        |        |        |        |        |        |
| Net cost to PBS (-\$)                                      | 4      | 4      | 4      | 4      | 4      | 4      |
| Net cost to MBS <sup>a</sup> (-\$)                         | 4      | 4      | 4      | 4      | 4      | 4      |
| Net cost to Government (-\$)                               | 4      | 4      | 4      | 4      | 4      | 4      |

Source: Sections 4.2-4.5, pp 160-185 of the submission

<sup>a</sup> Includes cost offsets due to displaced intravenous administrations of ravulizumab, cost offsets due to reduced blood transfusions, additional cost of therapeutic venesections for treatment of iron overload and additional cost of vaccine administrations

The redacted values correspond to the following ranges

<sup>1</sup><500

<sup>2</sup>500 to < 5,000

<sup>3</sup>\$10 million to <\$20 million

<sup>4</sup>\$0 to < \$10 million

6.98 The submission estimated net savings to the PBS of \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, a total saving of \$0 to < \$10 million over 6 years. The estimated net savings to the PBS/MBS was net cost saving in Year 1, increasing to net cost saving in Year 6, a total saving of net cost saving over 6 years.

6.99 The submission claimed that the listing of pegcetacoplan is not expected to increase the size of the PNH market, therefore any uncertainties in the model are unlikely to result in any additional cost to Government. This claim was reliant on the assumption that patients switching from a C5 inhibitor to pegcetacoplan would otherwise continue to receive treatment with a C5 inhibitor. The ESC considered this assumption was appropriate and that pegcetacoplan was not likely to increase the size of the treated population.

- 6.100 The submission claimed the [REDACTED] [REDACTED] approach and benefits associated with pegcetacoplan treatment are expected to be cost saving on an individual patient basis. The [REDACTED] [REDACTED] approach was reliant on the assumption of equivalent pricing between eculizumab and ravulizumab, which may not be appropriate given the effective price of ravulizumab is likely to include cost offsets due to reduced administrations. Cost offsets in the submission are likely to be overestimated due to the inappropriate inclusion of cost offsets associated with displaced use of iron chelation therapies and inadequately justified assumptions surrounding reduced treatment administration costs and reduced blood transfusions. The pre-PBAC response stated the sponsor remains committed to work with the Department of Health to ensure a pegcetacoplan on the PBS would be at least [REDACTED] if not [REDACTED]
- 6.101 The submission assumed no administration costs associated with pegcetacoplan as all patients would be self-administering treatment at home. It is unclear what proportion of patients would opt for home-based self-administration given the complex method of administration and potential safety risks associated with dosing errors. There are likely to be increased MBS costs associated with the administration of pegcetacoplan in healthcare settings, particularly given the frequency of administration (twice weekly or every 3 days). The ESC noted the expert opinion in the PSCR that with a small amount of instruction, all patients in the clinical trials were able to use the device to administer the product successfully.

### **Quality Use of Medicines**

- 6.102 The submission stated that the sponsor will be establishing a patient support program for patients who have been prescribed pegcetacoplan. The objectives of this program include the provision of the mechanical pumps and monthly consumables to individual patients at no additional cost, the provision of training to patients and carers on the use of the pumps and administration of pegcetacoplan and follow-up of patients during the first 2 months of therapy to ensure they are comfortable with the use of the pump and medication, through an external nurse vendor.
- 6.103 The submission stated that the sponsor is committed to working with the TGA on the development of the controlled distribution system and educational program, in accordance with the risk management plan for pegcetacoplan. The submission stated that a long-term safety and efficacy extension study for pegcetacoplan is currently being conducted (PASS study, expected completion late 2022) and the results will be shared with the TGA when available.
- 6.104 There are currently no data available on the management of breakthrough haemolysis events in patients treated with pegcetacoplan. There is currently no consensus on the severity of these events in the published literature and it is unclear how these events will be managed in practice.

## **Financial Management – Risk Sharing Arrangements**

- 6.105 No risk-sharing arrangement was proposed in the submission.
- 6.106 The PBAC noted that in the July 2021 consideration of ravulizumab a risk sharing arrangement was considered appropriate to manage any residual uncertainty associated with the cost to government of listing eculizumab and ravulizumab on the PBS (paragraph 7.17, ravulizumab PSD, July 2021 PBAC meeting).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommended pegcetacoplan, for the treatment of adults with paroxysmal nocturnal haemoglobinuria (PNH) who have inadequate clinical response to treatment with eculizumab or ravulizumab. The PBAC considered the evidence presented demonstrated a benefit compared to eculizumab in short-term haematological outcomes. However, the PBAC considered the economic model provided was not reliable for decision-making and hence the cost-effectiveness of pegcetacoplan could not be assessed.
- 7.2 The PBAC noted the input from individuals, health care professionals and organisations that described an unmet clinical need despite the current availability of the C5 inhibitors (i.e. eculizumab and ravulizumab).
- 7.3 The PBAC considered the proposed place in therapy, as treatment for PNH patients with an inadequate clinical response or intolerance to a C5 inhibitor, was appropriate.
- 7.4 The PBAC noted that no other second-line treatment to C5 inhibitor therapy was available. The PBAC considered eculizumab and ravulizumab were appropriate comparators as, given the nature of PNH, they would continue to be used in this population following an inadequate response. The PBAC noted that both eculizumab and ravulizumab were listed on the PBS in March 2022.
- 7.5 The primary clinical evidence supporting the clinical claim was the PEGASUS trial (N= 80) comparing pegcetacoplan with eculizumab. The PBAC noted that at the completion of the 16-week randomised controlled period, treatment with pegcetacoplan was associated with a statistically significant improvement in haemoglobin (Hb) level compared to eculizumab in the absence of transfusions (see Table 5). Numerical improvements in reticulocyte count and quality of life (associated with fatigue) were noted for pegcetacoplan (see Table 5), and the PBAC also considered that while pegcetacoplan likely improved transfusion avoidance, the magnitude of improvement varied over time (see paragraph 6.28). The PBAC considered the evidence presented supported a benefit in short-term haematological outcomes. The PBAC noted that no evidence to support non-inferiority in terms of long-term outcomes (including prevention of thrombosis or improved survival) was presented in the submission. The PBAC agreed with the ESC that the long-term clinical

data for pegcetacoplan was unlikely to be forthcoming for some time and thus the long-term relative benefit to C5 inhibitors was difficult to measure. The PBAC also recalled that its recommendation for ravulizumab relied on similar short-term outcomes comparative to eculizumab (see paragraph 6.34). Overall, the PBAC considered that while uncertain, the claim of non-inferior comparative effectiveness to the known benefits of eculizumab treatment in this population was reasonable.

- 7.6 The PBAC noted the higher rate of haemolysis events that led to treatment discontinuations in the pegcetacoplan arm during the randomised and cross-over periods (see Table 6). However, the PBAC considered that the requirement for all patients enrolled in the PEGASUS trial to be stable on eculizumab at baseline made safety comparisons difficult as patients would be less likely to have adverse events related to eculizumab. The PBAC agreed with the ESC that relative to the original eculizumab study (TRIUMP), the eculizumab toxicity profile was similar to pegcetacoplan. Overall, the PBAC considered that the claim of non-inferior comparative safety was uncertain but reasonable.
- 7.7 The submission presented a cost-utility analysis based on data from the PEGASUS trial and other modelled variables. Overall, the PBAC considered that the model was not reliable for decision making and hence the cost-effectiveness of pegcetacoplan could not be assessed (refer to paragraph 6.76). Issues with the model included:
- The structure limited the attribution of costs and benefits based on transfusion status and Hb level alone without adequately accounting for other disease-related complications;
  - The difference in the distribution of patients across the alive health states between treatment arms were primarily driven by time spent in the optimal health state and was the driver of the cost savings and improved quality of life associated with pegcetacoplan. The time spent in the defined health states was informed by transition probabilities that could not be validated during the evaluation as the source of the analysis was not provided;
  - The assumption that all PNH patients, regardless of treatment, have the same mortality rate as the general population was unlikely to be clinically plausible;
  - The assumption that patients receiving pegcetacoplan do not require chelation therapy for iron overload was not appropriate; and
  - The use of the health state utilities derived from EORTC QLQ-C30 scores given the instrument is specifically used to assess the health-related quality of life of cancer patients.
- 7.8 The PBAC noted that the submission proposed that pegcetacoplan be listed using a || approach with ravulizumab and/or eculizumab (see Table 7). In addition, the submission proposed that pegcetacoplan be considered at least non-inferior in efficacy and safety to ravulizumab and eculizumab. With ravulizumab and eculizumab considered appropriate comparators (see paragraph 7.4), the PBAC considered a cost-

minimisation approach likely an appropriate way forward in this rare condition.

- 7.9 As ravulizumab is dosed every 8 weeks the PBAC considered it would be the C5 inhibitor most likely to be replaced in clinical practice now that it is PBS listed and hence the appropriate base case comparator for any future cost-minimisation analysis. The PBAC considered use of ravulizumab in a cost-minimisation analysis also addressed concerns regarding the assumption made by the submission that each prescription provides 1 dose (see paragraph 6.577). The PBAC considered that dosing for ravulizumab over a 12-month maintenance period should be consistent with that accepted by the Committee for this agent in July 2021 (see paragraph 6.577). The PBAC noted that pegcetacoplan dosing in the  $QALY$  calculation was based on the 16-week randomised controlled period of the PEGASUS trial only. The PBAC noted that the proportion of patients in which the pegcetacoplan dose was escalated increased beyond 16 weeks (see paragraph 6.78). The PBAC considered dosing of pegcetacoplan over the 48-week period was more likely to reflect clinical practice and equi-effective doses with ravulizumab could be calculated over this longer time period. The PBAC noted that the  $QALY$  approach presented in the submission did not include offsets for pegcetacoplan for reduced administration costs or reductions in iron overload treatment or blood transfusions. The PBAC considered exclusion of such offsets from a cost-minimisation analysis appropriate due to the uncertainty of the cost-effectiveness of C5 inhibitors in patients with an inadequate clinical response to these agents. In addition, the PBAC considered the sponsor's 10% price rebate for the initial 4-week treatment phase appropriate to ensure no additional cost is associated with patients switching from C5 inhibitor treatment to pegcetacoplan. The PBAC noted ATAGI advice that it would be reasonable to recommend vaccination prior to pegcetacoplan against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B (HIB). The PBAC noted that for the treatment of PNH, eculizumab is listed in the medical risk conditions for vaccines currently listed on the NIP for meningococcal only, and not pneumococcal disease or HIB. The PBAC considered that the additional costs to Government for vaccination against pneumococcal disease and HIB should be included as additional costs associated with pegcetacoplan in the cost-minimisation approach. Finally, the PBAC considered that the calculation of prices should be based on the approved ex-manufacturer price (AEMP) rather than dispensed prices that include fees and mark-ups.
- 7.10 In terms of the financial estimates, the PBAC agreed with the submission that, outside of the grandfathered patients participating in a patient access program, pegcetacoplan would not increase the total treated PNH population as patients switching from a C5 inhibitor would otherwise continue to receive such treatment. The PBAC noted that grandfathered patients were already included within the prevalent population estimates. However, the PBAC considered the assumption that only patients treated with ravulizumab would receive iron chelation therapies for iron overload inappropriate and considered the cost offsets for reduced blood transfusions inadequately justified. As such, the PBAC considered the cost offsets overestimated.

- 7.11 The PBAC noted that no risk sharing arrangement was proposed in the submission. The PBAC considered it would likely be appropriate for pegcetacoplan to be included in the current risk sharing arrangement for eculizumab and ravulizumab.
- 7.12 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for pegcetacoplan using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.
- As per paragraph 7.9, a cost-minimisation analysis versus ravulizumab that: i) uses dosing for ravulizumab accepted by the Committee in July 2021; ii) bases pegcetacoplan dosing on that reported over 48-weeks in the PEGASUS trial; iii) does not include cost offsets for pegcetacoplan; iv) includes the sponsor proposed % price rebate for pegcetacoplan for the initial 4-week treatment phase; v) incorporates the costs of vaccination against pneumococcal disease and HIB; and vi) uses AEMP.
  - Revised financial estimates incorporating revised pricing for the CMA and the issues raised in paragraph 7.10 addressed.
- 7.13 The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.
- 7.14 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The sponsor had no comment.