6.11 PEGCETACOPLAN, Solution for subcutaneous infusion 1,080 mg in 20 mL, Empaveli®, Swedish Orphan Biovitrum Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Highly Specialised Drugs Program), Authority Required (Written) listing for pegcetacoplan for the treatment of patients aged 12 years and older with complement 3 glomerulopathy (C3G) or primary immune complex membranoproliferative glomerulonephritis (IC-MPGN).

1.2 The submission claimed that there is a clinical need for disease-modifying treatments for C3G and primary IC-MPGN as current treatment options are limited to supportive measures (aimed at reducing proteinuria and controlling blood pressure), and non-specific immunosuppressive therapies.

1.3 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care.

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

Component	Description
Population	Patients aged ≥12 years with C3G or primary IC-MPGN with native kidneys or disease recurrence following a kidney transplant
Intervention	Pegcetacoplan 1,080 mg in 20 mL twice weekly subcutaneous infusion for adults and adolescents with ≥50 kg body weight. Weight-based dosing is recommended in adolescents with <50 kg body weight [a]
Comparator	Main comparator: standard of care consisting of RAAS blockade (ACEI/ARB), SGLT2i and lifestyle measures, with or without immunosuppressive therapies (corticosteroids, mycophenolate mofetil) Near market comparator: iptacopan 200 mg orally twice daily
Outcomes	Reduction in proteinuria and stabilisation/slowed decline in eGFR leading to delay/avoidance of end stage kidney disease and related improvements in survival and quality of life
Clinical claim	Pegcetacoplan is superior in terms of efficacy and non-inferior in terms of safety compared to standard of care Pegcetacoplan is likely to be superior in terms of efficacy compared to iptacopan. No clinical claim was made regarding comparative safety

Source: Table 1-1, p15 of the submission

Abbreviations: ACEI/ARB, angiotensin converting enzyme inhibitor or angiotensin receptor blocker; C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; RAAS, renin-angiotensin-aldosterone-system; SGLT2i, sodium glucose co-transporter 2 inhibitor

[a] Adolescents with 35 to <50 kg body weight: twice weekly starting with a first dose of 648 mg then 810 mg subsequently; adolescents with 30 to <35 kg: twice weekly starting with 540 mg for the first two doses then 648 mg subsequently

2 Background

Registration status

2.1 Pegcetacoplan was submitted under the TGA parallel process. The TGA clinical evaluation report and Delegate's overview were available at the time of PBAC consideration.

2.2 The proposed indication for pegcetacoplan (Empaveli®) is for the treatment of adults and adolescents aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN).

2.3 The draft product information for pegcetacoplan 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. ATAGI advice would be required to extend access to these vaccines on the National Immunisation Program (NIP) for the requested PBS listing.

2.4 Pegcetacoplan was approved by the FDA in July 2025 for the treatment of adult and paediatric patients aged 12 years and older with C3G or primary IC-MPGN, to reduce proteinuria.

2.5 Pegcetacoplan (Empaveli®) is currently TGA-approved for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).

Previous PBAC consideration

2.6 Pegcetacoplan had not previously been considered by PBAC for this indication.

2.7 At the November 2025 PBAC meeting, the PBAC did not recommend iptacopan for the treatment of adults with C3G with either native kidneys or disease recurrence following a kidney transplant (PBAC outcomes, November PBAC 2025 meeting[1]). The PBAC reviewed the clinical evidence comparing the effectiveness and safety of iptacopan versus standard of care, noting that it is possible that iptacopan is more effective for some patients in terms of slowing progression to end-stage kidney disease. However, the PBAC noted limitations with evidence in the submission (based on short-term changes in proteinuria and no significant difference in estimated glomerular filtration rate) did not allow confidence to determine the extent to which iptacopan would delay kidney transplant or dialysis in patients with C3G. The clinical evidence also showed that iptacopan is less safe than standard of care due to increased risk of infection. The PBAC considered that the benefits claimed by the sponsor to justify its requested price were improbable and not supported by the

[1] Pharmaceutical Benefits Scheme (PBS) | Recommendations made by the PBAC – November 2025

clinical evidence in the submission. The PBAC considered that the cost-effectiveness of iptacopan had not been established.

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

3 Requested listing

3.1 The proposed listing is shown below with changes suggested by the Secretariat in italics/strikethrough.

Initial/Grandfather treatment phase:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
PEGCETACOPLAN					
~~Pegcetacoplan, C3G or pIC-MPGN, solution for subcutaneous infusion; 1.08 g/20 mL injection, 20 mL vial~~ *Pegcetacoplan 1,080 mg/20 mL injection; 20 mL vial*	NEW (Public) NEW (Private)	8	8	3	Empaveli
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – *Public/Private* (Code HB)					
Prescriber type: ☒ Medical Practitioners					
Benefit type: ☒ Authority Required *(FULL assessment) in writing only via OPA/post/HPOS upload*) ~~(in writing only via OPA/post/HPOS upload)~~					
Authority type: ☒ Complex Authority Required (CAR)					
Prescribing rule level:					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Caution: This drug increases the risk of encapsulated bacterial infections. Consult the approved ~~Product Information~~ *PI* for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection.					
Administrative Advice *Complement inhibitors are defined as eculizumab, ravulizumab or iptacopan*					
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. 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* *Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)* *Alternatively applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*					
Administrative Advice:					

Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use.
Restriction Summary 1 / Treatment of Concept: 1A
Indication: C3G or primary immune complex membranoproliferative glomerulonephritis (pIC-MPGN)
Treatment Phase: Initial treatment
Clinical criteria:
Patient must not have received prior treatment with this drug for this condition
AND
Clinical criteria:
Treatment must not be in combination with another Complement inhibitor
AND
Clinical criteria:
Patient must have a confirmed diagnosis of primary C3G or pIC-MPGN established by kidney biopsy
AND
Clinical criteria:
Patient must not have an eGFR less than 30 mL/min/1.73 m2
AND
Clinical criteria:
Patient must not be undergoing dialysis
Treatment criteria:
Must be treated by a nephrologist with experience in glomerular diseases; or
Must be treated by a non-specialist medical physician who has consulted a nephrologist on the patient's drug treatment details.
Population criteria:
Patient must weigh at least 30 kg
Population criteria:
Patient must be aged 12 years and older
AND
Prescribing Instructions: *The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include:* *(1) details of the proposed prescription(s); and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
Prescribing Instructions: ~~Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use~~. At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided: (i) uPCR (mg/g) (ii) eGFR (mL/min/1.73 m^2)
Prescribing Instructions: *An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.*
Prescribing Instructions: *At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information.*
Restriction Summary 2 / Treatment of Concept: 2A

Indication: C3G or primary immune complex membranoproliferative glomerulonephritis (pIC-MPGN)
Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – Grandfather arrangement
Clinical criteria:
Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of listing]
AND
Clinical criteria:
Treatment must not be in combination with another Complement inhibitor
AND
Clinical criteria:
~~Patient must not have received any treatment for this condition prior to commencing non-PBS-subsidised treatment with this drug~~ *Patient must not have received any treatment with pegcetacoplan for this condition prior to commencing non-PBS-subsidised treatment*
AND
Clinical criteria:
Patient must have a confirmed diagnosis of primary C3G or pIC-MPGN established by kidney biopsy
AND
Clinical criteria:
Patient must have experienced a clinical improvement as a result of treatment with this drug
AND
Clinical criteria:
Patient must not have had an eGFR less than 30 mL/min/1.73 m2 prior to commencing non-PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not be undergoing dialysis
Treatment criteria:
Must be treated by a nephrologist with experience in glomerular diseases; or
Must be treated by a non-specialist medical physician who has consulted a nephrologist on the patient's drug treatment details.
Population criteria:
Patient must weigh at least 30 kg
Population criteria:
Patient must be aged 12 years and older
AND
Prescribing Instructions: *The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include:* *(1) details of the proposed prescription(s); and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
Prescribing Instructions: ~~Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use~~. At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided: (i) uPCR (mg/g) (ii) eGFR (mL/min/1.73 m^2)

Prescribing Instructions: *An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.*
Prescribing Instructions: *At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information.*
Administrative advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*
Prescribing Instructions: *A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a grandfathered patient must qualify under the Subsequent continuing treatment criteria.*

First Continuing/Subsequent continuing treatment phase:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
PEGCETACOPLAN					
~~Pegcetacoplan, C3G or pIC-MPGN, solution for subcutaneous infusion; 1.08 g/20 mL injection, 20 mL vial~~ *Pegcetacoplan 1,080 mg/20 mL injection; 20 mL vial*	NEW (Public) NEW (Private)	8	8	5	Empaveli
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – *Public/Private* (Code HB)					
Prescriber type: ☒ Medical Practitioners					
Benefit type: ☒ Authority Required *(FULL assessment) in writing only via OPA/post/HPOS upload*) ~~(in writing only via OPA/post/HPOS upload)~~					
Authority type: ☒ Complex Authority Required (CAR)					
Prescribing rule level:					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
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. 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* *Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)* *Alternatively applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*					
Administrative Advice: *Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use.*					
Caution: This drug increases the risk of encapsulated bacterial infections.					

Consult the approved ~~Product Information~~ *PI* for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection.
Administrative Advice *Complement 5 (C5) inhibitors are defined as eculizumab or ravulizumab*
Restriction Summary 3 / Treatment of Concept: 3A
Indication: C3G or primary immune complex membranoproliferative glomerulonephritis (pIC-MPGN)
Treatment Phase: First continuing *treatment*
Clinical criteria:
Treatment must not be in combination with another Complement inhibitor
AND
Clinical criteria:
Patient must have received PBS-subsidised treatment with this drug for this condition under the 'Initial' *or 'Grandfather'* restriction
AND
Clinical criteria:
Patient must not be undergoing dialysis
AND
Clinical criteria:
~~Patient must have experienced a clinical improvement as a result of treatment with this drug~~
Patient must have experienced clinical improvement as a result of treatment with this drug; or
Patient must have experienced a stabilisation of the condition as a result of treatment with this drug
Treatment criteria:
Must be treated by a nephrologist with experience in glomerular diseases; or
Must be treated by a non-specialist medical physician who has consulted a nephrologist on the patient's drug treatment details.
Population criteria:
Patient must weigh at least 30 kg
Population criteria:
Patient must be aged 12 years and older
AND
Prescribing Instructions: *The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include:* *(1) details of the proposed prescription(s); and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
Prescribing Instructions: ~~Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use.~~ At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided: (i) uPCR (mg/g) (ii) eGFR (mL/min/1.73 m^2)
Prescribing Instructions: *An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.*
Prescribing Instructions: *At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information. A maximum of 5 repeats may be requested.*

Restriction Summary 4 / Treatment of Concept: 4A
Indication: C3G or primary immune complex membranoproliferative glomerulonephritis (pIC-MPGN)
Treatment Phase: Subsequent continuing *treatment*
Clinical criteria:
Treatment must not be in combination with another Complement inhibitor
AND
Clinical criteria:
Patient must have received PBS-subsidised treatment with this drug for this condition under the 'First Continuing' or 'Subsequent continuing' treatment restrictions
AND
Clinical criteria:
Patient must not be undergoing dialysis
AND
Clinical criteria:
Patient must have experienced clinical improvement as a result of treatment with this drug; or
Patient must have experienced a stabilisation of the condition as a result of treatment with this drug
Treatment criteria:
Must be treated by a nephrologist with experience in glomerular diseases; or
Must be treated by a non-specialist medical physician who has consulted a nephrologist on the patient's drug treatment details.
Population criteria:
Patient must weigh at least 30 kg
Population criteria:
Patient must be aged 12 years and older
AND
Prescribing Instructions: *The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include:* *(1) details of the proposed prescription(s); and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
Prescribing Instructions: ~~Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use.~~ *At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided:* *(i) uPCR (mg/g)* *(ii) eGFR (mL/min/1.73 m^2)*
Prescribing Instructions: *An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.*
Prescribing Instructions: *At the time of the authority application, medical practitioners must request the appropriate number of vials for 4 weeks supply per dispensing as per the Product Information. A maximum of 5 repeats may be requested.*

3.2 The sponsor proposed a special pricing arrangement with an effective AEMP per vial of $[redacted] and a published AEMP per vial of $4,343.86.

3.3 The requested initial treatment restriction includes 3 repeats, providing up to 16 weeks of treatment. The submission claimed that this provides sufficient time on

treatment for patients to demonstrate response, with VALIANT trial data showing that change in proteinuria in the pegcetacoplan arm appears to plateau from Week 16 of the trial. The evaluation considered it is unclear whether 16 weeks is a reasonable timepoint for assessment of response. The UpToDate guidelines for C3G suggest that response should be assessed after 6 months of therapy. The Sub-Committees noted that in both randomised controlled trials for pegcetacoplan and iptacopan, proteinuria plateaued at approximately 16 weeks, however outcomes were assessed at 6 months. The Sub-Committees considered that 16 weeks is likely to be an appropriate duration of treatment to demonstrate response in UPCR.

3.4 The proposed restriction is narrower than the proposed TGA indication as it requires eligible patients to be of a minimum weight, have a minimum level of kidney function, and not be undergoing dialysis. The Sub-Committees noted that these criteria were consistent with the trial and considered that pegcetacoplan would not be expected to benefit those with advanced chronic kidney disease, which was appropriately captured by the eGFR criterion. The Sub-Committees considered that the criterion stating that patients are not undergoing dialysis may not be needed for the initial listing as the criterion "Patient must not have an eGFR less than 30 mL/min/1.73 m^{2}" would exclude patients undergoing dialysis.

3.5 The submission claimed the proposed age criterion (≥12 years and older) is aligned with the proposed TGA indication and the key trial, and that broader eligibility was not pursued due to a lack of supporting evidence. The evaluation considered it was unclear whether the proposed minimum age is appropriate, or if the listing should be age agnostic. The Sub-Committees highlighted that there were no data in patients less than 12 years.

3.6 The proposed restriction does not differentiate between patients with native kidneys and those with disease recurrence following a kidney transplant. The Sub-Committees considered it would be appropriate to have separate restrictions for those with native kidneys and post-transplant patients. The Sub-Committees considered that eligibility should include biopsy-proven disease recurrence in kidney transplant patients.

3.7 The proposed restriction is broader than the key trial population that required evidence of active renal disease based on C3c staining intensity 2+ on kidney biopsy, or at least one marker of active disease in adolescents without a kidney biopsy (e.g. plasma sC5b-9 level above the upper limit of normal, serum C3 level below the lower limit of normal, haematuria or presence of C3 nephritic factor). The Sub-Committees considered that renal biopsy was sufficient for diagnosis, as captured in the proposed the criteria for initial and grandfather phase.

3.8 The evaluation noted that it is unclear whether decreased serum C3 levels (suggestive of an overactive complement pathway) should be considered as a clinical criterion in the restriction. Low serum C3 levels are not always present, and 27% of patients in the key trial of pegcetacoplan had normal levels. However, subgroup analyses based on the key trial suggest it is a potential treatment effect modifier, with numerically greater benefit in terms of proteinuria and eGFR in those with low C3 levels and less

certain magnitude of benefit in those with normal C3 levels defined as ≥90 mg/dL. Additionally, the iptacopan trial (APPEAR-C3G) required a C3 level of <77mg/dL at entry. The Pre-Sub-Committee Response (PSCR) stated the sponsor did not consider it appropriate to require decreased serum C3 as a mandatory restriction criterion as the VALIANT trial did not restrict enrolment to low-C3 patients and that treatment benefit was demonstrated in the broader population. The Sub-Committees noted that the subgroup analysis was based on small patient numbers and agreed with the sponsor that C3 levels should not form part of the restriction as it remains highly uncertain whether C3 levels are a treatment effect modifier.

3.9 The key trial excluded patients with evidence of severe, irreversible kidney scarring (defined as >50% global glomerulosclerosis or interstitial fibrosis on kidney biopsy). The Sub-Committees considered the eGFR criteria would exclude patients with advanced scarring and therefore an additional criterion was not needed.

3.10 The lack of a clinical criterion requiring a minimum level of proteinuria is inconsistent with the key trial which required elevated proteinuria levels based on 24-hour proteinuria ≥1.0 g/day or first morning sample UPCR ≥1.0 g/g. The PSCR disagreed with introducing a minimum level of proteinuria given the heterogeneity and progressive nature of C3G/primary IC-MPGN and evidence from VALIANT demonstrating consistent benefit across all baseline proteinuria levels. The Sub-Committees considered that a criterion requiring proteinuria ≥1.0 g/day should be present in the initial treatment restriction, consistent with the trial population. The pre-PBAC response agreed that it would be reasonable to include a minimum proteinuria threshold, consistent with the VALIANT trial population.

3.11 The lack of a treatment criterion requiring concomitant use of supportive measures is inconsistent with recommendations in published guidelines and the key trial that required stable and optimised use of ACEI/ARB and/or SGLT2 inhibitors. The Sub-Committees agreed with the evaluation that a treatment criterion should be included requiring continued use of supportive measures as appropriate (optimised use of ACEI/ARB +/- SGLT2). Although patients in the trial were allowed to be on stable doses of other immunosuppressants (e.g. mycophenolate mofetil, tacrolimus, low dose corticosteroids) the Sub-Committees considered that pegcetacoplan is likely to replace immunosuppressants (see also paragraph 4.9). The pre-PBAC response agreed that inclusion of this criterion was reasonable.

3.12 The submission proposed a first continuing restriction which requires patients to have experienced a clinical improvement as a result of treatment with pegcetacoplan. The submission claimed that the use of broad terminology was intentional given potential variation in individual response measured by proteinuria or eGFR. There is currently no consensus in published guidelines on objective measures of response in this disease. The Sub-Committee and the evaluation considered it would be more appropriate to state that patients must have clinical improvement or stabilisation of the condition given the progressive nature of the disease. The PSCR agreed that the restriction should specify that patients must demonstrate clinical improvement or

stabilisation of disease for first continuing treatment, given the progressive nature of C3G and primary IC-MPGN. The Sub-Committees noted that this may negate the need for separate first and subsequent continuing restrictions. The Sub-Committees also considered it was appropriate for pegcetacoplan to be discontinued once patients commence dialysis or undergo kidney transplant. The pre-PBAC response noted that the sponsor was not supportive of prescriptive start/stop rules beyond assessment of clinical response.

3.13 The submission stated that patients treated with pegcetacoplan must be monitored for proteinuria (first morning void urine protein-creatinine ratio, FMV UPCR) and renal function (estimated glomerular filtration rate, eGFR); consistent with the required provision of UPCR and eGFR results in the proposed restrictions for initial and first continuing treatment, however no objective measures are mentioned in the restriction. The Sub-Committees noted that these are standard routine measures to assess kidney disease and determine treatment response; however it is unclear whether the results need to be captured in the Authority application to exclude potential use in patients with stage 4/5 CKD not yet on dialysis.

3.14 The submission requested grandfathering provisions for patients treated with pegcetacoplan for C3G or primary IC-MPGN prior to PBS listing. The submission stated that up to < 500 patients would be receiving pegcetacoplan for treatment of these conditions through clinical trials or compassionate access by the time of PBS listing.

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

4 Population and disease

4.1 C3G and primary IC-MPGN are rare kidney diseases that share a similar underlying disease pathology and clinical course. The only pathologic distinction between C3G and primary IC-MPGN is through a kidney biopsy, where primary IC-MPGN is accompanied by deposition of immunoglobulin in addition to glomerular C3 deposition. Both C3G and primary IC-MPGN are characterised by glomerulonephritis (inflammation of the glomeruli - the filtering units of the kidneys), which can cause impairment of essential kidney functions and lead to kidney damage.

4.2 Diagnosis of these conditions requires a comprehensive approach utilising kidney biopsy, complement workup, genetic testing and evaluation of non-complement aetiologies. Both C3G and primary (or idiopathic) IC-MPGN are diagnoses of exclusion, when no underlying cause (infections, medications, systemic autoimmune diseases or cancer) can be identified. The establishment of a definitive diagnosis for these conditions can be challenging due to overlapping clinical and histopathological features and there are reports suggesting that patients can alternate between C3G and primary IC-MPGN over the course of their disease.

4.3 Clinical presentation varies between patients but typically includes proteinuria (protein in the urine), haematuria (blood in the urine) and other features associated

with kidney disease such as hypertension (high blood pressure), fatigue, oedema (fluid retention) and reduced urine output. Patients can have variable degrees of kidney impairment at presentation and variable rates of kidney function decline. Some patients have persistently low-grade proteinuria but maintain kidney function for a long time while others can present with rapidly progressive glomerulonephritis and have a poor prognosis. Patients with kidney failure usually require dialysis or kidney transplantation to stay alive. However, after transplantation, disease recurrence or graft loss is common due to the underlying condition.

4.4 There may be differences in terms of age at initial presentation, with some studies suggesting that patients with C3G typically experience disease onset at a younger age (20-30 years) while those with primary IC-MPGN are usually older at initial presentation (30-50 years) (Caravaca-Fontán 2025; Schaefer 2024 abstract). Adult-onset and paediatric-onset patients seem to differ clinically, with paediatric-onset disease typically presenting with more flare-prone, relapsing-remitting activity, while adult-onset disease more commonly shows gradual progression.

4.5 There are limited epidemiological data on C3G and primary IC-MPGN in Australia. A sponsor-commissioned systematic literature review and meta-analysis of global epidemiological studies (n=11, published between 2018 and 2025) suggests similar incidence and prevalence estimates for C3G (incidence 0.36 per million, prevalence 22.7 per million) and IC-MPGN (incidence 0.33 per million, prevalence 28.7 per million). It was noted that point prevalence estimates may be overestimated as they are unadjusted for disease progression and mortality, therefore a separate analysis was conducted using a mortality-correction factor applied to a smaller set of studies (n=5, published between 2020 and 2024) resulting in lower prevalence estimates for C3G (20.5 per million) and IC-MPGN (16.2 per million). There is inherent uncertainty in the available data due to inconsistent disease classifications that historically grouped membranoproliferative glomerulonephritis disorders as a single entity before recent changes in case definitions that distinguished complement-mediated from immune complex-driven disease.

4.6 Current recommendations for the treatment of C3G and primary IC-MPGN are based on expert consensus of general treatment approaches for membranoproliferative glomerulonephritis (MPGN), determined based on kidney biopsy lesions which are present in both C3G and IC-MPGN (KDIGO 2021, UpToDate March 2024 – Membranoproliferative glomerulonephritis: Treatment and Prognosis). More recently updated guidance for C3G were identified during the evaluation (UpToDate October 2025 - C3 glomerulopathies: Dense deposit disease and C3 glomerulonephritis).

4.7 In general, the recommendations were that all patients (regardless of disease severity), should receive supportive measures with ACEI/ARB, SGLT2 inhibitors, as well as blood pressure control. In patients with moderate to severe disease, it was suggested to add immunosuppressants (complement inhibitors, mycophenolate mofetil, corticosteroids), with escalation of immunosuppressants (pulse intravenous methylprednisolone followed by oral corticosteroids) in patients with rapidly

progressive crescentic disease. The October 2025 UpToDate recommendations suggest that for patients with moderate to severe disease (but without rapidly progressive disease), a complement inhibitor is preferred over other immunosuppressants.

4.8 Pegcetacoplan is a complement inhibitor that binds to complement protein C3 and its activation fragment C3b, thereby regulating the cleavage of C3 and downstream effects of complement activation. It is presumed that the therapeutic effects of pegcetacoplan are due to prevention of the downstream build-up of C3 proteins and resolution of inflammation in the kidneys.

4.9 The submission positioned pegcetacoplan as initial treatment in patients with native kidneys who have moderate to severe disease, displacing the use of immunosuppressant therapy with corticosteroids or mycophenolate mofetil. The submission claimed, based on expert advice, that complement inhibitors should be introduced early in the treatment algorithm, after a trial of RAAS blockade but before other immunosuppressants, given their targeted mechanism of action. The proposed place in therapy is inconsistent with the key trial, as pegcetacoplan was used as an add-on to background therapies in the vast majority of patients (91% on ACEI/ARB, 72% on immunosuppressants mainly mycophenolate mofetil and tacrolimus, and 40% on corticosteroids). The PSCR asserted that there was minimal change in the rate of background therapies in the trial due to the relatively short duration of the trial and requirements of trial protocol for patients to be on stable treatment. While not explicitly demonstrated in VALIANT, the PSCR asserted that stakeholder feedback from Australian nephrologists was that pegcetacoplan use in C3G and primary IC-MPGN would reduce treatment with immunosuppressant therapies over time, as these treatments are non-specific, have not demonstrated association with improved renal survival and have a negative impact on quality of life. The Sub-Committees agreed with the PSCR that in clinical practice use of pegcetacoplan would result in reduced use of immunosuppressive therapy, which is not considered to be effective, but is currently used, in the absence of alternative disease-modifying treatments.

4.10 The submission also positioned pegcetacoplan for the treatment of patients with C3G or primary IC-MPGN recurrence following a kidney transplant, in addition to supportive measures with or without immunosuppressants. The role of pegcetacoplan in post-transplant patients is uncertain based on limited data from VALIANT trial and NOBLE phase 2 study. The Sub-Committees considered that treatment of patients with C3G or primary IC-MPGN recurrence following a kidney transplant was clinically appropriate given the same mechanism of disease and noting the high clinical need for disease modifying treatments for these patients.

4.11 The submission's algorithm did not include measures of response or optimal duration of treatment with pegcetacoplan. No specific measures of response are mentioned in published guidelines, with authors of these guidelines highlighting that there are limited data informing therapeutic decisions in these disease areas. Based on clinical experience in C3G, the UpToDate authors state that response based on proteinuria

reduction and stable or improved kidney function is assessed after 6 months of therapy. In patients with response, therapy is continued for up to 2 years and those who do not respond may commence alternative treatments. Ongoing monitoring of urinary protein and kidney function is recommended after discontinuation of complement inhibitor therapy. In patients who experience relapse, complement inhibitor therapy should be re-started and continued indefinitely.

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

5 Comparator

5.1 The submission nominated standard of care as the main comparator. In patients with native kidneys, standard of care is represented by supportive measures that include renin-angiotensin system inhibition with ACEI/ARB, SGLT2 inhibitors and blood pressure control; as well as general immunosuppression (e.g. mycophenolate mofetil, corticosteroids) in patients with more active or progressive disease. In post-transplant patients with disease recurrence, standard of care includes supportive measures and adjustment of the post-transplant immunosuppression regimen. The Sub-Committees considered standard of care was an appropriate main comparator.

5.2 The submission nominated iptacopan as a near market comparator for adults with C3G, a subset of the requested population for pegcetacoplan. Iptacopan, an oral complement factor B inhibitor, was recently considered for treatment of adults with C3G by the PBAC at the November 2025 meeting but was not recommended.

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 described the natural history of the disease, with damage and inflammation to kidneys leading to loss of function over time, requiring dialysis and transplant. The clinician noted that patients often have a recurrence of disease following a transplant, which can mean they are not considered for another transplant. The clinician noted that chronic kidney disease is also associated increases in mortality due to cardiovascular disease and stroke, and also noted the mortality risk associated with transplant. The clinician responded to the Committee's questions regarding the relationship between proteinuria and progression to kidney disease and kidney failure. The clinician also discussed the steeper decline in EGFR in the control arm of the VALIANT study compared to the iptacopan study and disease registries. It was noted that although the reason for the difference is not certain it may have been impacted by the inclusion of higher risk patients who progress more quickly (e.g. adolescents who may have higher rates of

infection, primary IC-MPGN, post-transplant recurrent disease). The PBAC considered that the hearing was informative as it helped support the link between EGFR/proteinuria and kidney disease.

Consumer input

6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (4) and organisations (2) via the Office of Health Technology Assessment Consultation Hub. The inputs noted that C3G or primary IC-MPGN are described as ultra-rare diseases with no approved targeted therapies, with high rates of progression to end-stage kidney disease (≈50% within 10 years) and very high post-transplant recurrence rates (≈60–90%), often leading to graft loss. The inputs stated the diseases disproportionately affect adolescents and young adults, severely disrupting education, employment, family life, and mental health. Preventing or delaying kidney failure was framed as critical not only for survival, but for preserving dignity, independence, and long-term life opportunities in a predominantly young patient population. There was a strong emphasis on the importance of early and equitable access to effective treatment for this disease, noting that delayed diagnosis and delayed access to effective therapy can result in irreversible kidney damage and loss of transplant opportunities.

6.3 The inputs stated existing treatments (corticosteroids, mycophenolate mofetil, and supportive therapies such as Renin-Angiotensin-Aldosterone System (RAAS) inhibition have poor or inconsistent efficacy, with high rates of treatment failure. Additionally, the inputs stated that progression to dialysis is associated with profound physical, psychological, social and economic burden including fatigue, depression, infertility, repeated hospital attendance and long-term disengagement from the workforce. Clinicians reported that complement-targeting therapies represent a major advance, with pegcetacoplan described as having the strongest current evidence base. Real-world and compassionate-use experiences described by nephrologists include stabilisation of native and transplant kidney function, reduced hospitalisations and improved clinical and quality of life trajectories in some patients, including in patients with post-transplant recurrence. Although the subcutaneous pump administration of pegcetacoplan was acknowledged as inconvenient or cumbersome, clinicians reported that patients generally find it acceptable, particularly when compared with dialysis.

6.4 The inputs noted the primary safety concern of pegcetacoplan identified by clinicians is the risk of serious infections with encapsulated organisms, however, pegcetacoplan has been generally well tolerated. By contrast, clinicians emphasised current immunosuppressive regimens are associated with substantial and well-recognised long-term toxicities, including metabolic effects, osteoporosis, mood disturbance, infection risk and frequent hospital admissions. Several clinicians noted that long-term safety data for pegcetacoplan will remain important, given the likelihood of prolonged treatment.

6.5 The PBAC noted and welcomed the advice received in support of the PBS listing for pegcetacoplan from specialist organisation Australian & New Zealand Society of Nephrology (ANZSN) and consumer representative group Kidney Health Australia. The inputs echoed the same sentiments as the individual inputs. Both organisations noted that C3G and IC-MPGN most commonly affect young people, with many young patients reporting that they felt lonely and lacked a sense of belonging, missed classes as well as key milestones such as school camps, sports activities, events and group activities. The inputs noted the impacts of kidney disease on young people are further spread across the families of young people with kidney disease and have consequences on carers' mental health and financial resources. ANZSN noted that patients often experience significant delays in diagnosis which requires specialist nephrology services and diagnostic procedures. These delays to diagnosis can result in patients presenting at more advanced stages of disease with higher risk of progression to kidney failure. The organisations noted that many patients do not have access to any effective targeted therapies and are managed with untargeted immunosuppression or supportive treatments. The inputs emphasised that reducing the incidence of kidney failure can prevent physical, mental and emotional symptoms, prevent reduced quality of life and reduce carer burden and loss of income for patients and their families. The inputs also noted that pegcetacoplan is well tolerated and acceptable to patients despite the requirement for subcutaneous administration.

6.6 The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.7 The submission was based on a head-to-head randomised trial of pegcetacoplan versus placebo in patients with C3G or primary IC-MPGN (VALIANT).

6.8 The submission also presented a Bucher indirect comparison of pegcetacoplan (VALIANT) versus iptacopan (APPEAR-C3G) using placebo as a common reference. The submission used data from the APPEAR-C3G trial based on the adult cohort. The APPEAR-C3G trial is ongoing for the adolescent cohort, with expected completion in July 2026.

6.9 The submission excluded two open-label phase 2 studies of pegcetacoplan: a randomised controlled trial in post-transplant patients with recurrent C3G or IC-MPGN (NOBLE) and a single-arm study of pegcetacoplan in patients with C3G and other complement-mediated diseases (DISCOVERY). Reasons for exclusion of these studies were not provided in the submission. The DISCOVERY study recruited a small number of patients with C3G (n=8), with key results supportive of proteinuria reduction in patients treated with pegcetacoplan (mean change in 24-hour UPCR of 50.9% from baseline to Week 48) (Dixon 2023). The NOBLE study was a phase 2, multi-centre, open label randomised controlled trial of pegcetacoplan in post-transplant patients with recurrent C3G or IC-MPGN (pegcetacoplan n=10, placebo n=3) (Bomback 2024). The results suggested that pegcetacoplan was associated with reductions in C3c staining on renal biopsy and other biomarkers of disease activity in patients with post-

transplant disease recurrence. Outcomes based on proteinuria and eGFR levels were exploratory and inconclusive.

6.10 The submission excluded an ongoing long-term extension study of pegcetacoplan that included patients who completed 52 weeks of the VALIANT trial (VALE). The planned study duration is 2.5 years with expected completion in July 2027.

6.11 The submission excluded two ongoing studies of iptacopan: a randomised controlled trial in patients with primary IC-MPGN (APPARENT, expected completion May 2029) and a long-term extension study in patients with C3G or IC-MPGN (B12001B, expected completion May 2036). The submission also excluded a phase 2 study of iptacopan in patients with C3G glomerulopathy (X2202). No reason for exclusion of this study was provided.

6.12 Details of the included trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
VALIANT (APL2-C3G-310)	Apellis Pharmaceuticals (2024). AP2-C3G-310 clinical study report. A Phase 3, randomized, placebo-controlled, double-blinded, multicenter study to evaluate the efficacy and safety of pegcetacoplan in patients with C3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis	Internal study report
	Apellis Pharmaceuticals (2025). APL2-C3G-310 Week 52 clinical study report. A Phase 3, randomized, placebo-controlled, double-blinded, multicenter study to evaluate the efficacy and safety of pegcetacoplan in patients with C3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis	Internal study report
	Fakhouri et al (2025). Trial of pegcetacoplan in C3 glomerulopathy and immune-complex MPGN	New England Journal of Medicine 393:2210-20
APPEAR-C3G (CLNP023B12301)	Kavanagh et al (2025). Oral iptacopan therapy in patients with C3 glomerulopathy: a randomised, double-blind, parallel group, multicentre, placebo-controlled, phase 3 study	The Lancet 406 (10512): 1587-1598
	Novartis Pharmaceuticals (last update 2025). Study of efficacy and safety of iptacopan in patients with C3 glomerulopathy. (APPEAR-C3G)	ClinicalTrials.gov NCT04817618 (expected completion for adolescent cohort July 2026)

Source: Table 2-2, p42; Table A-1, Appendix A of the submission
Abbreviations: C3G, C3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis

6.13 The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence

Study	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Pegcetacoplan versus placebo						
VALIANT	124	Phase 3, randomised, double-blind, placebo-controlled trial (10-week screening, 26-week double-blind and 26-week open label periods)	Unclear	Patients aged ≥12 years and ≥30 kg diagnosed with native kidney or post-transplant recurrent C3G or primary IC-MPGN with evidence of active renal disease [a], eGFR ≥30 mL/min/1.73 m^2, first morning UPCR≥1.0 g/g and 24-hour proteinuria ≥1.0 g/day [b]. On stable and optimised regimen of ACEI/ARB and SGLT2 inhibitors, and stable doses of immunosuppressants and corticosteroids (max 20 mg/day of prednisone)	Primary: change in first morning UPCR Other: change in eGFR, proportion of patients achieving a composite renal endpoint (≤15% reduction in eGFR and ≥50% reduction in UPCR), change in histologic index activity score, change in quality of life measures	Baseline characteristics, change in UPCR, change in eGFR, corticosteroid use, EQ-5D-5L index scores
Iptacopan versus placebo						
APPEAR-C3G	74	Phase 3, randomised, double-blind, placebo-controlled trial (3-month run-in, 6-month double-blind and 6-month open label extension periods)	Unclear	Patients aged ≥18 years diagnosed with native kidney C3G, eGFR ≥30 mL/min/1.73 m^2, first morning UPCR ≥1.0 g/g and reduced serum C3 (<0.85 LLN, <77 mg/dL). On maximally recommended/tolerated dose of ACEI/ARB and stable doses of other SGLT2 inhibitors, immunosuppressants, corticosteroids (max 7.5 mg/day of prednisone) and mineralocorticoid antagonists [c]	Primary: change in 24-hour UPCR Other: change in eGFR, proportion of patients achieving a composite renal endpoint (15% reduction in eGFR and ≥50% reduction in UPCR), change in histologic index activity score, change in quality of life measures	-

Source: Section 2.4, pp50-60 of the submission; APPEAR-C3G trial publication (Kavanagh 2025)
Abbreviations: C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; SGLT2, sodium glucose co-transporter 2; UPCR, urine protein-creatinine ratio
[a] Baseline kidney biopsy with at least 2+ C3c staining; or in adolescents without baseline renal biopsy, biomarkers/signs of active disease (plasma sC5b-9 above upper limit of normal, serum C3 below the lower limit of normal, haematuria, historical presence of C3 nephritic factor)
[b] Patients were excluded if there was evidence of kidney scarring (>50% glomerulosclerosis or interstitial fibrosis on kidney biopsy) or evidence of improving kidney disease during the screening period (>30% increase in eGFR or >50% decrease in proteinuria)
[c] Patients were excluded if there was evidence of rapidly progressive crescentic glomerulonephritis or kidney scarring (>50% interstitial fibrosis/tubular atrophy)

6.14 The risk of bias in the VALIANT trial was minimised by the randomised controlled study design and blinding. However, the trial publication noted that patients who received pegcetacoplan were older, had higher levels of proteinuria and a lower eGFR than those who received placebo (Fakhouri 2025). These differences introduce potential bias in terms of key outcomes related to proteinuria and eGFR although the impact is unclear.

6.15 The risk of bias in the APPEAR-C3G trial was minimised by the randomised controlled study design and blinding. However, the trial publication noted that patients in the iptacopan arm had higher levels of proteinuria and a lower eGFR than those in the

placebo arm (Kavanagh 2025). There were also differences in the distribution of C3G disease subtypes, with a higher proportion with dense deposit disease in the iptacopan arm compared to placebo. The impact of these differences on key outcomes in the trial is unclear.

6.16 The submission claimed the VALIANT and APPEAR-C3G trials shared similar trial designs and outcome definitions. However, the VALIANT trial population was broader as it included the following: adolescents, primary IC-MPGN, post-transplant recurrent disease, patients with serum C3 levels above 77 mg/dL (0.85 × lower limit of normal) and did not exclude those with signs of rapidly progressive crescentic glomerulonephritis. Both trials required stable and optimised use of supportive measures and other immunosuppressants.

6.17 Despite the inclusion of adolescents in the VALIANT trial, mean baseline age was similar to the APPEAR-C3G trial, ranging from approximately 24–30 years across treatment arms in both trials. There were also differences in sex distribution between the trials: the majority of patients in the VALIANT trial were female, and the majority of patients in the APPEAR-C3G trial were male.

6.18 A comparison of geometric means in both trials shows similar baseline 24-hour UPCR levels between VALIANT (pegcetacoplan 3.2 g/g, placebo 2.7 g/g) and APPEAR-C3G (iptacopan 3.3 g/g, placebo 2.6 g/g) although UPCR levels were higher in the treatment arms of both trials compared to placebo.

6.19 The submission noted that mean baseline eGFR was higher in APPEAR-C3G (89-99 mL/min/1.73 m^2) compared with VALIANT (78-87 mL/min/1.73 m^2), and a lower proportion of patients had eGFR <60 mL/min/1.73 m^2 (11-26% in APPEAR-C3G and 34% in VALIANT). The submission suggested that the APPEAR-C3G population could be at an earlier stage of disease, with better preserved kidney function compared to those in the VALIANT trial. However, the impact of these differences on key outcomes in the trials is uncertain.

6.20 A comparison of annualised eGFR slopes between APPEAR-C3G and VALIANT shows substantial differences in the rate of eGFR decline across pre- and post-randomisation periods between trials (see Table 6). There were particularly notable differences in eGFR declines during the double-blind period, which was considerably worse in the placebo arm of VALIANT compared to APPEAR-C3G. The data also show contrasting eGFR trajectories in the placebo arms, which worsened after randomisation in VALIANT but improved after randomisation in APPEAR-C3G. The reasons for these differences could not be determined from the available data.

6.21 Patients in APPEAR-C3G had lower mean baseline serum C3 levels (31-34 mg/dL) compared to VALIANT (59 mg/dL). Subgroup data from the VALIANT trial suggest that serum C3 level is a potential treatment effect modifier, with greater proteinuria reduction and improvements in eGFR in patients with low C3 levels compared to patients with normal C3 levels.

6.22 Overall, the exchangeability of the VALIANT and APPEAR-C3G trials is uncertain given the differences in population and disease characteristics.

6.23 The submission claimed that the VALIANT trial population, background therapy and outcomes assessed are well-aligned with Australian practice. The submission acknowledged potential differences between the VALIANT trial and Australian setting in terms of baseline eGFR. The submission claimed that kidney function was relatively well-preserved for the majority of the trial population (66% with eGFR ≥60 mL/min/1.73 m^2) but in practice, there may be a broader spread, with some patients having lower baseline eGFR levels. The submission claimed that the absolute benefit of pegcetacoplan may be smaller in patients with less renal reserve (who are closer to kidney failure). The evaluation stated that applicability of the VALIANT trial population to the proposed PBS population is uncertain given the lack of data in the Australian setting.

6.24 The risk profile of patients in the VALIANT trial was not well-characterised in the submission. The rate of eGFR decline in the placebo arm of the VALIANT trial was substantially worse than in the APPEAR-C3G trial and disease registries (UK RaDaR registry and Spanish GLOSEN registry). The reasons for this were not explored in the submission, with no explanation provided in the trial report. The applicability of the disease trajectory of patients in the VALIANT trial to the proposed PBS population is uncertain. The Sub-Committees considered that the rate of eGFR decline in the placebo arm of the VALIANT trial was faster than expected in clinical practice and that there was no clear explanation for the rapid eGFR decline in the placebo arm in the VALIANT trial.

Surrogate measures

6.25 The submission claimed that reductions in proteinuria and stabilisation or slowed decline in eGFR are surrogate measures for delay or prevention of progression to end stage kidney disease (ESKD) in C3G and primary IC-MPGN and presented a surrogate framework in the submission.

- Proteinuria: Epidemiological evidence presented in the submission was supportive of a biological rationale linking elevated proteinuria with an increased risk of ESKD. Observational data also suggest a positive relationship between proteinuria reduction and reduced risk of progression to ESKD. However, definitions of proteinuria varied between studies in terms of magnitude of proteinuria reduction (i.e. range of percentage reductions and proteinuria thresholds). There are no randomised controlled trials supporting a quantitative relationship between proteinuria reduction and changes in the risk of ESKD in patients with C3G or primary IC-MPGN.
- Change in eGFR: No epidemiological data were presented to support an association between changes in eGFR and the risk of ESKD among patients with C3G or IC-MPGN. Observational data in patients with chronic kidney disease (CKD) show a positive association between a slower decline in eGFR and reduced risk of kidney disease progression leading to ESKD. There are no randomised controlled trials supporting a quantitative relationship between

changes in eGFR and changes in the risk of ESKD in patients with C3G or primary IC-MPGN.

6.26 The PSCR acknowledged that there are currently no direct data demonstrating long-term outcomes for pegcetacoplan in C3G and primary IC-MPGN and that more robust long-term evidence is unlikely to be forthcoming due to the ultra-rare nature and relative recency of identification of these diseases. The response reiterated that the value of eGFR and proteinuria as indicators of more severe disease and increased disease progression risk are well established, and considered improvements observed in VALIANT provide a strong rationale for anticipated long-term clinical benefit. The Sub-Committees considered that biological plausibility and epidemiological evidence support proteinuria and eGFR decline as very important prognostic variables for kidney disease progression in C3G and primary IC-MPGN. The Sub-Committees considered that data to demonstrate treatment-related changes in proteinuria or eGFR would result in a quantifiable change in the risk of kidney failure in these patients would be difficult to attain.

Comparative effectiveness

6.27 Table 4 presents results for the primary endpoint of change in log-transformed ratio of first morning urine (FMU) urinary protein-creatinine ratio (UPCR) at Week 26 in the VALIANT trial.

Table 4: Change in log-transformed FMU UPCR (g/g) at Week 26

Treatment arm	Baseline, Geo-mean (95% CI)	Week 26 ratio to baseline (95% CI) [a, b]	Treatment difference, % reduction (95% CI) [a]
Pegcetacoplan N = 63	2.48 (2.10, 2.93)	0.33 (0.25, 0.43)	**68.1 (57.3, 76.2)**
Placebo N = 61	2.02 (1.71, 2.38)	1.03 (0.91, 1.16)	

Source: Table 2-16, p61 of the submission; Table 14.5.1 *post hoc* tables and Table 14.1.14.1.3 of the VALIANT trial report
Abbreviations: CI, confidence interval; FMU, first morning urine; Geo-mean, geometric mean; UPCR, urinary protein-creatinine ratio
[a] Based on a mixed model with repeated measures analysis of log-transformed geometric mean FMU UPCR
[b] Geometric means and ratios are estimated by exponentiated least square means and differences. The difference from baseline to Week 26 was measured using an equal-weighted average over Weeks 24, 25 and 26 in the trial

6.28 Treatment with pegcetacoplan was associated with a statistically significant reduction in FMU UPCR compared to placebo at Week 26 from baseline. Sensitivity analyses using alternative imputation approaches (missing at random, tipping point analysis) produced results that were consistent with the primary analysis. The change in proteinuria from baseline exceeded the nominated minimal clinically important difference of at least 50% reduction in proteinuria.

6.29 A post hoc analysis was conducted to analyse the change from baseline in log-transformed 24-hour UPCR. The geometric mean ratio at Week 24 compared to baseline was 0.313 (95% CI 0.235, 0.417) for pegcetacoplan and 0.915 (95% CI 0.783, 1.070) for placebo, a relative reduction of 65.8% ($p < 0.001$) for pegcetacoplan versus placebo.

6.30 Treatment effects on proteinuria were sustained at Week 52 during the open-label extension period of the trial.

6.31 Table 5 presents results for responder analyses based on percentage changes in eGFR and UPCR at Week 26.

Table 5: Responder analyses based on key secondary endpoints at Week 26

Outcome	Pegcetacoplan N = 63	Placebo N = 61	Odds ratio (95% CI)
Composite renal endpoint, n/N (%) - ≤15% decrease in eGFR - ≥50% reduction in FMU UPCR	31/63 (49.2) 43/63 (68.3) 38/63 (60.3)	2/61 (3.3) 36/61 (59.0) 3/61 (4.9)	**27.5 (6.1, 123.8)** [a]
≥50% reduction in FMU UPCR, n/N (%)	38/63 (60.3)	3/61 (4.9)	**30.9 (8.4, 113.8)** [a]

Source: Table 2-19, p65 of the submission; Table 21, p121; Table 25, p25 of the VALIANT trial report
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FMU UPCR, first morning urine protein-creatinine ratio
[a] The logistic model included treatment group as independent variable and adjusted for baseline values, disease type, and stratification factors. A composite strategy was used where the response status at or after the occurrence of any of the intercurrent events was regarded as non-responder. Participants with missing outcome values other than intercurrent events were regarded as non-responder
Bolded results are statistically significant, adjusted for multiplicity using a fixed sequence testing hierarchy

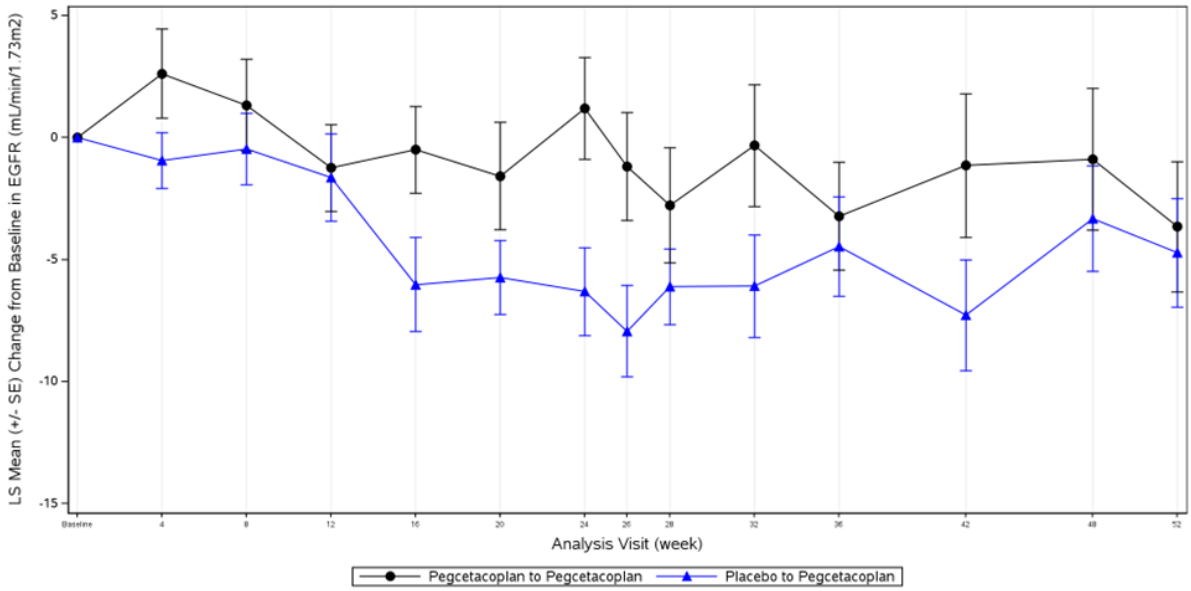
6.32 Results for the composite renal endpoint were statistically significant based on the fixed sequence testing hierarchy, in favour of pegcetacoplan compared to placebo (relative difference 45.6%; 95% CI 21.2, 70.0). The difference was driven by the proportion of patients achieving ≥50% reduction in first morning UPCR at 26 weeks (relative difference 52.7%; 95% CI 29.2, 76.2).

6.33 Results at 52 weeks during the open-label period were supportive of sustained treatment effects, with similar proportions in both arms achieving the composite renal endpoint compared to baseline (38.1% in patients originally randomised to pegcetacoplan and 36.1% in patients who switched from placebo to pegcetacoplan). The results in the pegcetacoplan arm were numerically lower compared to Week 26, with similar reductions in those achieving individual components of ≤15% reduction in eGFR (61.9%) and ≥50% reduction in FMU UPCR (50.8%).

6.34 An exploratory analysis based on the proportion of patients achieving proteinuria <1 g/day (measured by 24-hour urine) at 26 weeks was also in favour of pegcetacoplan (36.5%) compared to placebo (11.5%), a difference of 21.1% (95% CI 3.7, 38.5) between arms.

6.35 Figure 1 is a plot of change in eGFR during the 26-week randomised controlled period and up to Week 52 of the open-label extension period of the VALIANT trial.

Figure 1: Plot of mean change in eGFR (mL/min/1.73 m^2) over 52 weeks in the VALIANT trial



Source: Figure 2.5, p66 of the submission
Abbreviations: eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error
Note: A mixed effects model of repeated measures including fixed categorical effect for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline eGFR, is utilised to analyse the mean change from baseline to week 26 in eGFR. Missing data will be imputed implicitly in a hypothetical strategy under the assumption of missing at random

6.36 From baseline to Week 26, the least squares mean change in eGFR was -1.5 mL/min/1.73 m2 with pegcetacoplan and -7.81 mL/min/1.73 m2 with placebo (least squares mean difference 6.31 mL/min/1.73 m2, 95% CI 0.5, 12.1, relative difference -80.8%, p<0.03). No formal statistical testing was performed as hierarchical testing was stopped after the third secondary endpoint (C3G histologic index activity score). The pre-PBAC response argued that the absence of significant changes in C3G-HI (now known to be insensitive to changes in disease course due to therapy) confounds interpretation of eGFR change and that although differences in eGFR can only be labelled as nominally significant there were clinically meaningful differences between the treatment arms.

6.37 At Week 52, change in eGFR from baseline was -3.65 mL/min/1.73 m^2 in the pegcetacoplan/pegcetacoplan group showing a similar rate of eGFR decline to the randomised period of the trial. The pre-PBAC response also noted that 100-week data from VALIANT show pegcetacoplan-treated patients demonstrated sustained eGFR stabilisation, with a mean increase of +1.0 mL/min/1.73 m² (5.4% increase in eGFR) from baseline, supporting durability of renal function preservation over approximately two years of treatment.

6.38 An exploratory analysis was conducted to assess the annual rate of change in eGFR (mL/min/1.73 m^2/year). A pretreatment eGFR slope was calculated based on historical data from up to 3 years prior to screening and the same pretreatment slope was used for both treatment groups. The trial report noted that the estimation of the pretreatment slope was limited by data sparseness, as only 30% of patients had more

than 1 year of retrospective data. The results of the analysis are summarised in Table 6.

Table 6: Annualised eGFR slope analysis, mL/min/1.73 m²/year (95% CI)

	Pegcetacoplan N = 63	Placebo N = 61
Pre-treatment slope	-4.27 (-8.27, -0.27) [a]	
Post-treatment slope	-3.61 (-9.38, 2.16)	-16.58 (-22.31, -10.85)
Difference pre- vs post-treatment	0.66 (-5.36, 6.69)	-12.31 (-17.98, -6.64)
Difference between treatment groups	12.97 (5.27, 20.67)	

Source: Table 40, p144 of the VALIANT trial report

[a] Same pre-treatment slope assumed for both arms

Note: eGFR slope estimates were calculated using a generalised linear mixed model including a fixed effect for disease type, and stratification factors (transplant status, availability of baseline renal biopsy), a common intercept, a pretreatment (either pegcetacoplan or placebo) slope, and a change in the slope by arm after treatment

6.39 The analysis shows the annualised eGFR slope during the post-treatment period (i.e. double-blind period) was slightly improved in the pegcetacoplan arm but substantially worse in the placebo arm when compared to the pre-treatment period. The trial report noted that the post-treatment eGFR slopes were consistent with the key secondary endpoint, showing a slower decline for pegcetacoplan compared to placebo. The analysis showed a substantial difference between treatment arms when comparing the pre- and post-treatment differences in annualised eGFR slopes, in favour of pegcetacoplan versus placebo.

6.40 The validity of results from the eGFR slope analysis could not be determined given limited documentation regarding methods of analysis. For example, no justification was provided for the assumption of no difference in eGFR slopes between arms during the pre-treatment period.

6.41 The analysis also suggests very rapid eGFR decline in the placebo arm after randomisation. The reasons for this were not explored in the submission, with no explanation provided in the trial report.

6.42 The trial also assessed disease-specific and health-related quality of life measures, with no apparent differences between arms in terms of Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), EQ-VAS, Kidney Disease Quality of Life (KDQOL-36), Productivity, and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) questionnaires. A numerically higher proportion of patients in the pegcetacoplan arm reported an improvement based on change in Patient Global Impression of Change (PGIC) and Work (very much improved, much improved, and minimally improved) compared to those on placebo.

6.43 Health state utility values in the economic model were derived using trial-based EQ-5D-5L index scores, however no documentation of the original scores from the trial was provided with the submission.

Indirect comparison with iptacopan

6.44 The submission conducted Bucher indirect comparisons based on key outcomes from VALIANT and APPEAR-C3G using data from the whole trial population. Sources and values used in the submission's analyses were difficult to verify due to poor documentation in the submission.

6.45 Table 7 presents results of indirect comparisons for proteinuria reduction based on log-transformed geometric mean UPCR ratio to baseline, based on first morning urine and 24-hour urine samples.

Table 7: Bucher indirect comparison between pegcetacoplan and iptacopan for the primary outcome of proteinuria reduction (based on first morning urine in VALIANT and 24-hour urine in APPEAR-C3G)

Trial	Pegcetacoplan	Placebo	Iptacopan	Difference in ratio (95% CI)
Log-transformed geometric mean FMU UPCR ratio to baseline (95% CI)				
VALIANT	0.33 (0.25, 0.43) N=63	1.03 (0.91,1.16) N=61	-	0.32 (0.24, 0.43)
APPEAR-C3G	-	1.00 (0.77, 1.31) N=36	0.68 (0.52, 0.87) N=38	0.67 (0.47, 0.97) [a]
			Indirect comparison of pegcetacoplan versus iptacopan	**0.47 (0.30, 0.76)**
Log-transformed geometric mean 24-hour UPCR ratio to baseline (95% CI)				
VALIANT	0.31 (0.24, 0.42) N=63	0.92 (0.78, 1.07) N=61	-	0.34 (0.25, 0.48)
APPEAR-C3G	-	1.08 (0.88, 1.31) [a] N=36	0.70 (0.57, 0.85) [a] N=38	0.65 (0.49, 0.86)
			Indirect comparison of pegcetacoplan versus iptacopan	**0.53 (0.34, 0.82)**

Source: Table A-7, p129 of the submission; Kavanagh 2025 publication and p12 of the supplementary appendix
Abbreviations: CI, confidence interval; FMU, first morning urine; UPCR, urine protein-creatinine ratio
[a] Updated during the evaluation based on results reported in p12 of the Kavanagh 2025 appendix.
Bolded results were statistically significant

6.46 The analyses suggest that pegcetacoplan was associated with statistically significantly greater relative reductions in UPCR compared to iptacopan (53% for first morning sample, difference in ratio of 0.47; and 47% for 24-hour sample, difference in ratio of 0.53).

6.47 Table 8 presents results of the indirect comparison for mean change in eGFR (mL/min/1.73 m^2).

Table 8: Bucher indirect comparison between pegcetacoplan and iptacopan based on change in eGFR from baseline (mL/min/1.73 m^2)

Trial	Pegcetacoplan Mean (95% CI)	Placebo Mean (95% CI)	Iptacopan Mean (95% CI)	Treatment difference (95% CI)
VALIANT	-1.50 (-5.90, 2.90) N=63	-7.81 (-11.57, -4.05) N=61	-	6.31 (0.50, 12.12)
APPEAR-C3G	-	-0.86 (-4.36, 2.64) N=36	1.30 (-2.14, 4.73) N=38	2.16 (-2.75, 7.06)
			Indirect comparison of pegcetacoplan versus iptacopan	4.16 (-3.45, 11.76)

Source: Table A-8, p130 of the submission; p7, Kavanagh 2025 publication; p12, Kavanagh 2025 supplementary appendix
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate

6.48 There was no apparent difference between pegcetacoplan and iptacopan in terms of mean change in eGFR from baseline. The results should be interpreted with caution given the substantially different rates of eGFR decline in the common reference arms of the trials.

6.49 The submission acknowledged that there were limitations to the Bucher indirect analyses due to key differences between the VALIANT and APPEAR-C3G trial populations including age group, disease type, transplant status and baseline serum C3 level. The submission claimed that these differences introduce uncertainty in the

reliability of results from the Bucher analysis as it assumes that the trials are comparable without significant differences in effect modifiers. To address these concerns, the submission performed post hoc sensitivity analyses across subgroups in the VALIANT trial based on disease type (C3G versus IC-MPGN), age (adults, adolescents), sex (male, female) and serum C3 levels (<77 mg/dL, ≥77 mg/dL) and combinations that most closely align to APPEAR-C3G (adults with C3G, serum C3 <77 mg/dL, and both).

6.50 The submission claimed that disease type and age were not treatment effect modifiers. No discussion was provided regarding the subgroup analysis according to sex. The submission claimed that baseline serum C3 level was a potential treatment effect modifier, with greater magnitude of benefit for both proteinuria reduction and slowing eGFR decline in those with serum C3 <77 mg/dL compared to those with serum C3 ≥77 mg/dL. The validity of results from these analyses could not be determined due to insufficient documentation in the submission.

Comparative harms

6.51 All patients in the VALIANT trial received mandatory vaccination against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae type b.

6.52 Table 9 presents a summary of adverse events during the randomised period of the VALIANT trial.

Table 9: Summary of key adverse events in the trials

	Pegcetacoplan N = 63		Placebo N = 61	
	Incidence, n (%)	Events, n	Incidence, n (%)	Events, n
Any AE	53 (84.1)	390	57 (93.4)	380
Treatment-related AE	25 (39.7)	125	26 (42.6)	134
Infusion-related AE	21 (33.3)	110	16 (26.2)	124
Serious AE	6 (9.5)	9	6 (9.8)	10
AE leading to treatment discontinuation	2 (3.2)	2	2 (3.3)	2
AE leading to dose interruption	7 (11.1)	13	12 (19.7)	29
AE leading to study discontinuation	1 (1.6)	1	1 (1.6)	1
Fatal AE	1 (1.6)	1	0	0
Rejection episodes	0	0	0	0
Graft loss	0	0	0	0
AE of special interest				
Thrombocytopaenia	0	NR	1 (1.6)	NR
Severe infection	2 (3.2)	NR	0	NR
Hypersensitivity	8 (12.7)	NR	5 (8.2)	NR
Severe acute kidney injury	1 (1.6)	NR	1 (1.6)	NR

Source: Table 2-24, p69, Table 2-30, p75 of the submission
Abbreviation: AE, adverse event; NR, not reported

6.53 The overall frequency of any adverse events was high in both treatment arms of the trial. The most commonly reported adverse events (≥40% in either arm) were infections and infestations (pegcetacoplan 55.6%, placebo 44.3%) and general disorders and administration site conditions (pegcetacoplan 46.0%, placebo 47.5%). Treatment with pegcetacoplan was associated with more frequent reports of pyrexia,

nasopharyngitis, influenza, nausea, cough, contusion, acute kidney injury and fatigue compared to placebo.

6.54 The frequency of serious adverse events was similar between arms. The most common serious adverse event was acute kidney injury, reported by one patient in the pegcetacoplan arm and 2 patients in the placebo arm. One patient in the pegcetacoplan arm experienced a serious adverse event of pyrexia that was considered to be treatment related. There was one fatal event in the pegcetacoplan arm (respiratory failure due to COVID-19 pneumonia); this was assessed as not related to treatment.

6.55 Due to the mechanism of action of pegcetacoplan, route of administration and relevance to C3G and primary IC-MPGN, the trial protocol defined thrombocytopaenia, severe infections, hypersensitivity and severe acute kidney injury as adverse events of special interest. Most events were mild to moderate in severity, except for severe infections (influenza, COVID-19) and acute kidney injury; these events were assessed as not related to treatment.

6.56 The incidence of anti-pegcetacoplan peptide antibody response was 22.6%, with few patients developing anti-pegcetacoplan neutralising antibodies (3.2%). The incidence of anti-polyethylene glycol antibody response was 11.3% (3.2% treatment-emergent and 8.1% treatment-boosted). Post hoc analyses by anti-pegcetacoplan peptide antibody response did not show an association between a positive antibody response and increased frequency of adverse events.

6.57 The frequency of any adverse event during the open-label period was slightly lower in both pegcetacoplan/pegcetacoplan and placebo/pegcetacoplan arms compared to the randomised period. There were no notable differences in the occurrence of common adverse events during the open label period compared to the randomised period. The most common serious adverse events were acute kidney injury (3 patients), dehydration (2 patients) and pyrexia (2 patients). There was one serious infection by encapsulated bacteria (Streptococcus pneumoniae, assessed as not treatment-related) and one serious infection of herpes zoster meningoencephalitis that was assessed as possibly related to pegcetacoplan.

6.58 The submission provided a Periodic Safety Update Report (PSUR) (14 November 2023 to 13 November 2024 reporting period). No new safety signals were identified during the reporting period. During the reporting period, the classification of anaphylaxis (serious allergic or hypersensitivity reactions) was amended from an important potential risk to an important identified risk. Additional important potential risks include serious infections due to encapsulated bacteria, discontinuation-related intravascular haemolysis, immunogenicity, malignancies and haematological abnormalities and potential long-term effects of polyethylene glycol accumulation. Missing information includes patients starting treatment with bone marrow failure (excluded from PNH trials), use in pregnancy and long-term safety (>1 year).

Benefits/harms

6.59 On the basis of direct evidence presented in the submission, in patients with native kidneys or post-transplant recurrence of C3G or primary IC-MPGN, for every 100 patients treated with pegcetacoplan compared to placebo:

- Approximately 55 additional patients would have at least a 50% reduction in proteinuria (a marker of kidney injury) at 26 weeks (see Table 5).
- There would be no apparent difference in quality of life measures at 26 weeks (see para 6.42).
- There would be approximately 11 additional patients with infections and infestations (2 patients with severe infections) over 26 weeks (see Table 9 and para 6.53).

Clinical claim

6.60 The submission described pegcetacoplan as superior in terms of efficacy compared to standard of care. The evaluation considered this claim was reasonable in terms of short-term reductions in proteinuria but was inadequately supported in terms of changes in eGFR decline and longer-term reductions in the risk of progression to end-stage kidney disease. The Sub-Committees agreed with the evaluation that the claim of superior efficacy compared to standard of care was reasonable with regard to proteinuria. The PSCR disagreed with the evaluation's assertion that there was no apparent difference in eGFR decline between treatment arms of the VALIANT trial, noting that the difference in LS mean change in eGFR from baseline was considered clinically relevant and had a nominal p-value of 0.03 (not formally tested for statistical significance due to the hierarchical endpoint testing strategy). The Sub-Committees considered that the duration of the double-blind phase of the trial was likely too short and the sample size too small to clearly demonstrate any change in eGFR decline.

6.61 The submission described pegcetacoplan as non-inferior in terms of safety compared to standard of care. This evaluation considered this claim was inappropriate given the known increased risk of infections with pegcetacoplan treatment, particularly due to encapsulated bacteria. Additionally, patients treated with pegcetacoplan are at risk of infusion-related adverse events that would otherwise not occur in patients receiving standard of care. The Sub-Committees agreed with the evaluation that a claim of inferior safety would be appropriate.

6.62 The submission described pegcetacoplan as superior in terms of efficacy compared to iptacopan. The evaluation considered it was unclear whether this claim was reasonable. Results of the indirect comparison suggest that pegcetacoplan may be superior in terms of short-term reductions in proteinuria but there was no apparent difference in terms of change in eGFR decline compared to iptacopan. However, there were limitations with the analysis due to differences between trial populations in terms of age, sex, disease type, transplant status and baseline serum C3 level. The Sub-Committees agreed with the evaluation that it was unclear whether the claim of

superior efficacy for pegcetacoplan compared with iptacopan was reasonable given the limitations of the comparison.

6.63 The submission did not provide a clinical claim in terms of safety compared to iptacopan.

6.64 The evaluation noted the following issues with the clinical claims:

- There are concerns with the applicability of the trial to the Australian setting, particularly the rapid eGFR decline in the placebo arm that is substantially worse than the placebo arm of the APPEAR-C3G trial of iptacopan and in observational studies. The PSCR stated that the applicability concerns raised for the VALIANT trial largely reflect the heterogeneous population enrolled, which included adults and paediatric patients, as well as post-transplant recipients. The Sub-Committees considered that the eGFR decline in the placebo arm was faster than expected in clinical practice but that there was no clear explanation for the rapid eGFR decline in the placebo arm in the VALIANT trial. The Sub-Committees noted that there were several Australian centres included in the VALIANT trial and considered that it was unlikely that Australian patients would differ meaningfully from those included in the VALIANT trial.
- There are no data supporting long-term outcomes with pegcetacoplan such as delay or avoidance of end-stage kidney disease and associated survival benefits. There was biological plausibility and epidemiological evidence supporting proteinuria and eGFR as prognostic variables for kidney disease progression. However, there were no direct data demonstrating that treatment-related changes in proteinuria or eGFR would result in a quantifiable change in the risk of kidney failure in patients with C3G or primary IC-MPGN. The Sub-Committees noted that this data would be difficult to obtain for end stage renal disease patients, but considered proteinuria and eGFR decline to be very important predictors of outcome in this population.

6.65 The PBAC considered that the claim of superior comparative effectiveness over standard of care was adequately supported by the data for the surrogate measure of reduction in proteinuria, for which there is strong biologically plausibility for an impact on kidney disease. However, changes in eGFR were less certain, mainly due to the unexplained rapid decline in eGFR in the standard of care arm of VALIANT. The PBAC noted that there was no demonstrated change in QoL for pegcetacoplan.

6.66 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

6.67 The PBAC considered that the claim of superiority over iptacopan was not adequately supported by the data due to differences in the trial populations included in the VALIANT and APPEAR-C3G trials.

Economic analysis

6.68 The submission presented an economic evaluation of pegcetacoplan compared to standard of care for the treatment of patients aged 12 years or older with C3G or primary IC-MPGN with native kidneys or disease recurrence following a kidney transplant. The economic evaluation was based on the VALIANT trial with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.69 Key components of the economic evaluation are summarised in Table 10.

Table 10: Key components of the economic evaluation

Component	Description
Type of analysis	Cost effectiveness/cost utility analysis
Outcomes	Life years, quality adjusted life years
Time horizon	74 years (lifetime)
Methods used to generate results	Markov cohort analysis
Perspective	Health care system (inclusion of costs and QALY gains associated with redirected kidney transplants)
Treatments	Pegcetacoplan or standard of care therapies
Model structure	20 before transplant health states comprising of 15 CKD stage/UPCR combined health states and 5 kidney replacement therapy health states (transplant eligible or transplant ineligible haemodialysis/peritoneal dialysis and transplant); and 5 CKD stage/UPCR <1 combined tunnel states 18 post-transplant health states comprising of 15 CKD stage/UPCR combined health states and 3 kidney replacement therapy health states (haemodialysis, peritoneal dialysis and transplant); and 5 CKD stage/UPCR <1 combined tunnel states Death as an absorbing state
Cycle length	3 months (half-cycle correction)
Transition probabilities	Risks of treatment discontinuation according to UPCR level in the pegcetacoplan arm were assumed. Transition probabilities between UPCR levels were estimated from a regression model, developed from a post hoc analysis of patient-level data from the VALIANT trial. Transition probabilities between CKD stages (risk of CKD progression) were based on a post hoc analysis of patient-level data from the VALIANT trial to estimate the rate of eGFR decline according to UPCR levels. Mean eGFR declines were converted to transition probabilities by estimating the total time it would take to transition from the maximum eGFR to the minimum eGFR in each CKD stage. It was assumed that all patients reaching CKD stage 5 would transition to dialysis after one 3-month cycle. The estimated transition probabilities for UPCR and CKD stage were combined to derive transitions probabilities for the CKD/UPCR combined health states including the CKD/UPCR<1 tunnel states. Dialysis and transplant The submission assumed that 16.8% of patients on dialysis would be ineligible for kidney transplant. The remaining patients were assumed to be on haemodialysis or peritoneal dialysis, distributed according to dialysis modality received by patients in the US (Trivedi 2015). Patients on dialysis who are transplant eligible may undergo kidney transplantation. The probability of transplantation was derived from the median time on a waiting list for transplant reported in the Australia and New Zealand Dialysis and Transplant Registry (47th Annual Report, 2024). Following a kidney transplant, a one-off risk of graft failure was applied based on graft failures in the first year among US kidney transplant patients (Pruett 2021). Patients with graft failure were assumed to receive dialysis but remain transplant eligible. Patients with a successful graft were re-distributed across CKD stage 1 to 4 based on 1-year eGFR estimates among post-transplant patients in the US (Pruett 2021). The submission assumed that post-transplant patients with a successful graft would return to the

Component	Description
	initial distribution of UPCR levels in the model. In subsequent cycles, post-transplant patients with a successful graft were attributed the same transition probabilities between the CKD/UPCR combined health states as for the before transplant health states. All post-transplant patients who reach CKD stage 5 and commence dialysis were assumed to be eligible for subsequent transplants. Mortality and cardiovascular events Risks of cardiovascular events were based on a US study of the prevalence of stroke (Imoisili 2024) and a global study of the prevalence of heart failure (Bragazzi 2021). The source of the risk of myocardial infarction was not presented in the submission. The model also applied cardiovascular event risk multipliers, with increasing risk in later CKD stages (source not provided). All-cause mortality was estimated based on Australian life tables (Australian Bureau of Statistics 2022-2023) with additional risk multipliers for CKD stage and kidney replacement therapy health states based on a cost-effectiveness analysis of finerenone versus standard of care in patients with type 2 diabetes and chronic kidney disease (Quist 2025). Cardiovascular mortality was estimated based on predicted death rates for vascular disease from US life tables (actuarial study no. 116 published in 2002) with additional risk multipliers CKD stage and kidney replacement therapy health states (source not provided).
Utility values	UPCR health state disutilities were estimated based on post hoc analyses of EQ-5D-5L index scores in the VALIANT trial, mapped to EQ-5D-3L utility values (UK value set) (no documentation of the original scores or mapping were provided). UPCR health state disutility values were derived from a linear regression model fitted to the mapped EQ-5D-3L utility scores. CKD stage 1 and 2 health state utility values were estimated based on a post hoc analysis of VALIANT trial data (estimates could not be validated during the evaluation). CKD stage 3 and 4 utility values were based on a published systematic review of health state utility values in chronic kidney disease (Cooper 2020). Kidney failure health state utility values (CKD 5, haemodialysis, peritoneal dialysis, transplant) were based on a published systematic review of health state utility values in chronic kidney disease (Cooper 2020). The submission tested the impact of including a caregiver disutility in sensitivity analyses, based on a survey of EQ-5D-5L utility values in patients with CKD and their caregivers in the US (Esposito 2023, abstract only). The submission assumed no disutilities associated with treatment-related adverse events. Cardiovascular event disutility values were based on a cost-effectiveness analysis of finerenone versus placebo in patients with CKD and type 2 diabetes (Quist 2025) and a cost-effectiveness analysis of dapagliflozin versus placebo in patients with CKD (McEwan 2022). The QALY gain associated with redirected kidney transplants was based on an Australian economic analysis of early transplantation with a moderate quality kidney versus remaining on dialysis while on a waitlist for transplant (Senanayake 2020).
Costs	Pegcetacoplan drug costs were estimated based on the proposed effective price and assuming 90% dose intensity. Drug costs for standard of care (ACEI/ARB, corticosteroids, immunosuppressants and SGLT2 inhibitors) were based on published prices. The submission assumed no administration costs (all patients on pegcetacoplan would self-administer) and no vaccine costs (no justification provided). CKD stage/UPCR combined health state costs were estimated using values presented in a costing analysis of chronic kidney disease in Australia based on a Western Australian data linkage study using a 'bottom up' costing approach (Randall 2024), with adjustments according to UPCR level within each CKD stage derived from a retrospective study of US electronic health records in patients with IgA nephropathy (Lerma 2023). Costs of kidney replacement therapies were based on values used as inputs in a cost-effectiveness and budget impact analysis of implementing a 'soft opt-out' system for kidney donation in Australia (Senanayake 2022).

Component	Description
	The submission assumed no treatment-related adverse event costs. Costs for adverse events due to long-term corticosteroid use were based on estimates reported for low dose users in a systematic review of publications on the burden of long-term corticosteroid exposure (Rice 2017). Costs of acute cardiovascular events were estimated based on hospitalisation costs from inlier price weights for selected Australian Refined Diagnosis Related Groups (AR-DRGs) in the National Efficient Price Determination 2025-26 report. Long-term costs in patients with a stroke were estimated from an Australian study of the economic impact of stroke using a Markov decision analytic model (Kim 2024). Terminal care costs were based on expert opinion from an Australian Senate report (item 3.71 of the Parliament of Australia – Palliative care in Australia, Senate report 10 October 2012). Cost savings associated with redirected kidney transplant were based on an Australian economic analysis of early transplantation with a moderate quality kidney versus remaining on dialysis while on a waitlist for transplant (Senanayake 2020).
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3-1, p82; Sections 3.3-3.6, pp84-96 of the submission
Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; QALY, quality adjusted life year; SGLT2, sodium glucose cotransporter 2; UPCR, urine protein-creatinine ratio

6.70 Patients enter the model with chronic kidney disease and elevated proteinuria based on an assumed distribution across CKD stages 2 and 3 and an adjusted UPCR level distribution based on the VALIANT trial (4 combined health states of CKD 2/UPCR 1-3, CKD 2/UPCR <3, CKD 3/UPCR 1-3 and CKD 3/UPCR >3). In each 3-month cycle, patients can move to any UPCR health state (stay, improve or worsen) but can only stay or progress to a worse CKD stage. In each cycle, patients can also experience a non-fatal cardiovascular event or die due to cardiovascular or other causes. Patients who reach CKD stage 5 are assumed to receive conservative care for one cycle, after which all patients switch to haemodialysis or peritoneal dialysis. Patients on dialysis are either eligible or ineligible for transplant; those who are ineligible remain on dialysis until death. Patients who are eligible for transplant can either remain on dialysis or undergo a transplant. After transplantation, patients with a graft failure switch to dialysis but are eligible for subsequent transplants. Patients with a successful graft are redistributed across post-transplant CKD stages 1-4 according to the initial distribution across UPCR levels at the start of the model. Following the redistribution, patients can move to any UPCR health state (stay, improve or worsen) but can only stay or progress to a worse CKD stage based on the same rates as the starting population, before undergoing a transplant in the model.

All patients who have a transplant are assumed to be eligible for a subsequent transplant. Patients who undergo a subsequent transplant follow the same transitions as per the initial transplant in the model. Patients in the pegcetacoplan arm discontinue treatment when they commence dialysis.

6.71 The model structure is complex, with the inclusion of a large number of health states to track combined changes in CKD stage and UPCR level, use of kidney replacement therapies, cardiovascular events and corticosteroid use over time. The added complexity of UPCR health states, cardiovascular events and corticosteroid use

appears to have a limited impact on the results of the economic analysis; and the model is limited in its ability to track patients in more relevant health states such as those who had undergone a transplant (patients who undergo a single transplant cannot be distinguished from those with multiple transplants). The PSCR and pre-PBAC response accepted that the model structure was complex but considered this necessary to capture the clinically and economically relevant changes in disease progression over time. The sponsor asserted that the model submitted reflects the nature of these rare, chronic kidney conditions and aligns with the structure of the model submitted to NICE for pegcetacoplan for the treatment of C3G and primary IC-MPGN. The pre-PBAC response also noted that the model limitations relate primarily to uncertainty in the long-term evidence rather than the structure of the model.

6.72 The Sub-Committees noted that there were effectively 20 health states prior to transplant and 18 post-transplant health states and considered that the added complexity from the UPCR sub-states was not justified. The Sub-Committees noted that there was insufficient trial data to inform transitions between the health states in the model and therefore there were a number of sources informing transition probabilities that added to uncertainty in the modelled outcomes. The Sub-Committees noted the following issues identified in the Commentary with transition probabilities:

- Between uPCR categories: multiple regression models were used with current uPCR state as a dependent variable and independent variables for intervention, uPCR state at the previous visit, age, sex and disease type (C3G, primary IC-MPGN). The sub-committees considered the approach was not well justified.
- Between CKD stages 1-5: Four generalised linear regressions were used to derive eGFR transition probabilities. There were erratic changes in eGFR at each timepoint even within the same UPCR category, with values shifting unpredictably from improvement to decline to stabilisation. There was also data sparseness, with small sample sizes informing some values (e.g. the smallest subgroup consisted of 4 patients). The Sub-Committees noted that it was unclear whether the assumption of a linear decline in eGFR is appropriate given the relapsing/remitting nature of the disease.
- From CKD 5 – kidney replacement: sources were inadequately justified for: 100% patients transitioning to dialysis after CKD 5 for one 3 month cycle; the proportion on dialysis, the proportion ineligible for a kidney transplant and there were inconsistencies between the submission text and the model.
- Post transplant: the approach used to model the disease trajectory of patients after a transplant includes many assumptions and substantially underestimates the effectiveness of transplantation and resulted in an accelerated progression to kidney failure, with the approach biased in favour of pegcetacoplan.

- Inclusion of corticosteroid use, CVD events and mortality: based on poorly justified estimates, with multiple calculation errors for CVD mortality rates and estimates that could not be verified.

6.73 Treatment discontinuation rates in the model were poorly justified and assumed a higher rate than in the trial (assumed to be 5% per cycle in UPCR<1 and UPCR 1-3 health states and 80% per cycle in UPCR>3 health state) and resulted in a relatively short time on treatment in the model of 3.2 years. Treatment discontinuations were assumed to be permanent as patients could not re-initiate therapy.

6.74 The Sub-Committees noted that there were a number of issues with the utility values applied, as identified in the Commentary:

- The UPCR health states were based on post-hoc regression models fitted to trial data and could not be verified.
- The health state utility for CKD5 could not be verified from the reported source (Cooper 2020).
- The chosen utility value for the haemodialysis state was the lowest reported value from a systematic review and the selection of this value was not justified.

Overall, the Sub-Committees considered the approach to applying utilities was inconsistent, did not use preferred PBAC use of trial-based utilities where available, lacked face validity and was a key driver of the ICER.

6.75 The submission claimed that kidney transplants are a finite resource and that each kidney transplant avoided with pegcetacoplan treatment in C3G or primary IC-MPGN could be re-allocated within the healthcare system, to another patient outside the target population of the submission who may benefit from a kidney transplant. During the evaluation, the base case analysis was revised by excluding the additional costs and outcomes, which the Sub-Committees considered was appropriate.

6.76 Key drivers of the economic model are summarised in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Model structure	The model structure precluded the ability to explore the impact of differences in age, disease subtype, serum C3 levels and alternative assumptions regarding the effectiveness of transplant.	Unclear
Change in eGFR over time	A post hoc analysis was conducted using patient-level data from the VALIANT trial to estimate the rate of eGFR decline according to UPCR level based on cut-offs used for health states in the model (UPCR <1 g/g, UPCR 1-3 g/g and UPCR >3 g/g). Mean eGFR decline within each UPCR category was calculated as the mean difference between eGFR values at the current timepoint and eGFR values at the previous timepoint (3-monthly intervals). The post hoc analysis was used to inform the generalised linear regression model used to calculate the rate of eGFR decline used in the model. No justification was provided for the chosen regression model given all included variables (UPCR 1-3 g/g, UPCR >3 g/g, treatment arm) were not statistically significant. The R^2 was very low which indicated that the model was a poor predictor of differences in change in eGFR (explaining 2% of the variation).	High
Post-transplant transitions	Following a kidney transplant, the submission assumed a one-off risk of graft failure based on graft failures in the first year among kidney transplant patients in the US (Pruett 2021). Patients with a successful graft were re-distributed across CKD stages 1 to 4 based on a study of eGFR estimates at 1-year among post-transplant patients in the US (Pruett 2021). The approach assumes that most post-transplant patients have a lower-than-normal level of function (33% CKD 2, 52% CKD 3). The submission assumed that post-transplant patients would return to the baseline distribution of UPCR levels as per the key trial. This assumption was inappropriate as it inherently assumes that all post-transplant patients experience immediate disease recurrence. In subsequent cycles, post-transplant patients were attributed the same transition probabilities between the CKD/UPCR combined health states as for the before transplant health states. This approach was inadequately justified as no data were presented to inform the disease trajectory of the post-transplant population. The submission assumed that all post-transplant patients who are on dialysis would be eligible for subsequent transplants. This assumption was inappropriate as transplant eligibility is multi-factorial, and not all patients will be eligible or be considered for a subsequent transplant. Overall, the approach used to model the disease trajectory of patients after a transplant substantially underestimates the effectiveness of transplantation and resulted in an accelerated progression to kidney failure. This approach was biased in favour of pegcetacoplan.	High
Dialysis health state utility values	The submission estimated dialysis health state utility values from a systematic review of health state utility values in CKD (Cooper 2020). The estimates for haemodialysis (0.44) and peritoneal dialysis (0.53) were based on patients attending a renal unit in the UK (Lee 2005). The utility estimate used in the economic model for haemodialysis was the lowest reported value from the Cooper 2020 review (EQ-5D-3L utility scores: 0.44-0.75; mean estimate: 0.67). The submission did not provide any justification for the selected value.	High

Source: Constructed during the evaluation

Abbreviations: ANZDATA, Australian and New Zealand Dialysis and Transplant registry; C3G, C3 glomerulopathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; UPCR, urine protein-creatinine ratio

6.77 The submission assumed a 90% relative dose intensity for pegcetacoplan treatment, claiming that this was likely in a real-world setting. The dose intensity was applied as a reduction in treatment costs without commensurate reductions in treatment benefit. This was inappropriate as modelled treatment effects were based on 99% compliance in the trial.

6.78 The difference in total cost between treatment arms was primarily driven by pegcetacoplan drug costs. The incremental cost was partially offset by reduced disease management costs associated with delay/avoidance of kidney replacement therapies (dialysis and transplant).

6.79 The difference in health outcomes between treatment arms was primarily driven by increased time spent in earlier CKD stages and reduced time spent on haemodialysis (with relatively low utility values) in the pegcetacoplan arm compared to the SoC arm.

6.80 The results of the modelled economic evaluation are summarised in Table 12. The submission did not present a stepped analysis as requested in the PBAC guidelines.

Table 12: Results of the economic evaluation

Component	Pegcetacoplan	SoC	Increment
Revised base case			
Costs	$[redacted]	$1,195,334	$[redacted]
QALYs	9.66	8.93	0.73
		Incremental cost per QALY gained	**$[redacted][1]**

Source: Table 3-22, p101 of the submission; 'Pegcetacoplan CUA' Excel model provided with the submission
Abbreviation: QALY, quality adjusted life year; SoC, standard of care
The redacted values correspond to the following ranges:
[1] *$755,000 to < $855,000*

6.81 Based on the economic model, treatment with pegcetacoplan was associated with an incremental cost per QALY gained of $755,000 to < $855,000 compared to SoC for the treatment of C3G or primary IC-MPGN.

6.82 The submission claimed that a high incremental cost effectiveness ratio was reasonable given the high clinical need, rarity of the disease and young age of the affected population.

6.83 The evaluation and the Sub-Committees considered the cost-effectiveness estimate should not be considered reliable given uncertainties with modelled change in eGFR estimates based on the VALIANT trial that were substantially worse than in other studies of C3G/IC-MPGN, the assumption that all post-transplant patients (with a successful graft) have immediate disease recurrence which substantially underestimates the effectiveness of transplantation, inadequately justified dialysis utility values and limitations with the model structure that precluded the ability to explore the impact of differences in patient and disease characteristics.

6.84 The Sub-Committees noted the median time to death in the modelled population was 41.8 years in the pegcetacoplan arm and 41.5 years in the SoC arm (after accounting for baseline age, the median age at death in the model was approximately 68 years). The Sub-Committees considered it was unclear whether the modelled estimates were representative of the life expectancy of patients with C3G or primary IC-MPGN given the limited published data available to provide external validation.

6.85 The results of some of the key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 13.

Table 13: Sensitivity analyses

Analysis	Incremental cost	Incremental QALYs	ICER	% change
Revised base case	**$[redacted]**	**0.73**	**$[redacted][1]**	**-**
Scenario analysis including cost savings and QALY gains for redirected kidney transplants (submission's base case)	$[redacted]	0.99	$[redacted][2]	- [redacted]%
Discount rate (revised base case: 5% costs and outcomes)				
0%	$[redacted]	1.05	$[redacted][3]	- [redacted]%
3.5%	$[redacted]	0.80	$[redacted][1]	- [redacted]%
UPCR health states (revised base case: higher disease management costs in UPCR 1-3 and UPCR>3, UPCR disutility in UPCR 1-3 and UPCR>3, discontinuation rate 5% in UPCR<1 and UPCR 1-3 and 80% in UPCR>3)				
Remove difference in costs or utilities by UPCR level, equal discontinuation rate for all UPCR levels (5%)	$[redacted]	1.02	$[redacted][4]	+ [redacted]%
Change in eGFR per 3-month cycle (revised base case: pegcetacoplan no change in UPCR<1, -0.71 in UPCR 1-3 and -2.36 in UPCR>3; SoC -1.47 in UPCR<1, -3.05 in UPCR 1-3 and -4.70 in UPCR>3 based on trial data)				
eGFR decline for pegcetacoplan based on 25% of trial-based decline for SoC	$[redacted]	0.67	$[redacted][4]	+ [redacted]%
eGFR decline for pegcetacoplan based on 50% of trial-based decline for SoC	$[redacted]	0.53	$[redacted][5]	+ [redacted]%
eGFR decline for pegcetacoplan based on 75% of trial-based decline for SoC	$[redacted]	0.41	$[redacted][5]	+ [redacted]%
eGFR decline for SoC based on 125% of trial-based decline for pegcetacoplan	$[redacted]	0.48	$[redacted][5]	+ [redacted]%
eGFR decline for SoC based on 150% of trial-based decline for pegcetacoplan	$[redacted]	0.53	$[redacted][5]	+ [redacted]%
eGFR decline for SoC based on 175% of trial-based decline for pegcetacoplan	$[redacted]	0.57	$[redacted][5]	+ [redacted]%
eGFR decline for SoC based on mean change in SoC arm of the key trial of iptacopan (APPEAR-C3G; -3.08 mL/min/1.73 m^2/year applied as -0.77 per 3-month cycle) and trial-based relative difference for pegcetacoplan (19.2% of eGFR decline in SoC) [a]	$[redacted]	0.40	$[redacted][5]	+ [redacted]%
eGFR decline for SoC based on mean change in C3G patients in the RaDaR registry (-4.2 mL/min/1.73 m^2/year applied as -1.05 per 3-month cycle) and trial-based relative difference for pegcetacoplan (19.2% of eGFR decline in SoC) [a]	$[redacted]	0.45	$[redacted][5]	+ [redacted]%
eGFR decline for SoC based on mean change in IC-MPGN patients in the RaDaR registry (-3.3 mL/min/1.73 m^2/year applied as -0.83 per 3-month cycle) and trial-based relative difference for pegcetacoplan (19.2% of eGFR decline in SoC) [a]	$[redacted]	0.41	$[redacted][5]	+ [redacted]%
eGFR decline for SoC based on median change in C3G/IC-MPGN patients in the GLOSEN registry (-1.7 mL/min/1.73 m^2/year applied as -0.43 per 3-month cycle) and trial-based relative difference for pegcetacoplan (19.2% of eGFR decline in SoC) [a]	$[redacted]	0.32	$[redacted][5]	+ [redacted]%
Utility values (revised base case: 0.44 for haemodialysis and 0.53 for peritoneal dialysis based on a single source from the Cooper 2020 systematic review; healthcare perspective)				
Haemodialysis and peritoneal dialysis utility values based on the mean estimate for haemodialysis (0.67) from Cooper 2020	$[redacted]	0.49	$[redacted][5]	+ [redacted]%
Include caregiver disutility [b]	$[redacted]	0.90	$[redacted][6]	- [redacted]%

Source: Table 3-24, p102 of the submission; 'Pegcetacoplan CUA' Excel model provided with the submission
Abbreviations: C3G, C3 glomerulopathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoglomerulonephritis; QALY, quality adjusted life year; UPCR, urine protein-creatinine ratio;
[a] Based on estimates reported in Kavanagh 2025 (APPEAR-C3G), Masoud 2025 (RaDaR) and Caravaca-Fontán 2025 (GLOSEN). Estimated eGFR declines were applied equally across all UPCR health states
[b] Based on a survey of EQ-5D-5L utility values in patients with CKD and their caregivers in the United States (Esposito 2023, abstract only). The estimate was based on mean utility values reported for caregivers (0.81) and a matched general population sample (0.94).
The redacted values correspond to the following ranges:
[1] *$755,000 to < $855,000*
[2] *$455,000 to < $555,000*
[3] *$555,000 to < $655,000*
[4] *$855,000 to < $955,000*
[5] *> $1,055,000*
[6] *$655,000 to < $755,000*

6.86 The model is most sensitive to change in eGFR over time, time horizon, dialysis health state utility values and the inclusion of cost savings and QALY gains due to redirected kidney transplants. Costs and consequences associated with UPCR health states, cardiovascular events and corticosteroid use had a limited impact on the economic analysis.

6.87 Given the unnecessarily large number of health states included in the model, the Sub-Committees considered that sensitivity analyses removing UPCR disutilities (collapsing the separate UPCR sub-states) were informative. Further, given the sensitivity of the ICER to utility values, the Sub-Committee considered that multivariate sensitivity analyses using mean EQ-5D-3L utility values from Cooper (2020) and removing UPCR disutilities for all CKD stages would be informative. These analyses are provided in

6.88 Table 14.

Table 14: Additional sensitivity analyses

Analysis	Incremental cost	Incremental QALYs	ICER	% change
Revised base case	**$**	**0.73**	**$** [1]	**-**
No UPCR disutilities for CKD stages 3 to 5	$	0.69	$ [2]	+ %
No UPCR disutilities for all CKD stages	$	0.70	$ [1]	+ %
Scenario analysis using mean EQ-5D-3L utility estimates from Cooper 2020 (CKD 2: 0.85, CKD 3: 0.73, CKD 4: 0.74, CKD 5: 0.73, haemodialysis: 0.67, peritoneal dialysis: 0.57) and include UPCR disutilities for all CKD stages (-0.063 for UPCR levels >1 g/g)	$	0.40	$ [3]	+ %
Scenario analysis using mean EQ-5D-3L utility estimates from Cooper 2020 (CKD 2: 0.85, CKD 3: 0.73, CKD 4: 0.74, CKD 5: 0.73, haemodialysis: 0.67, peritoneal dialysis: 0.57) and no UPCR disutilities for all CKD stages (-0.063 for UPCR levels >1 g/g)	$	0.37	$ [3]	+ %

Source: Table 3.9.1 of the commentary and conducted for ESC DUSC

The redacted values correspond to the following ranges:

[1] *$755,000 to < $855,000*

[2] *$855,000 to < $955,000*

[3] *> $1,055,000*

6.89 The impact of differences in age, disease subtype, serum C3 levels and alternative assumptions regarding the effectiveness of transplant in the target population (e.g. not all patients experience disease recurrence, delay in disease recurrence, alternative rates of decline in kidney function) could not be explored due to limitations with model structure.

Drug cost/patient/year

Table 15: Drug cost per patient per year for pegcetacoplan

	VALIANT trial	Economic model	Financial estimates
Cost per 28 days (effective DPMQ for 8 × 1,080 mg vials)	-	$[redacted] [a]	$[redacted] [a]
Treatment adherence	99% [b]	90% [c]	90% [c]
Scripts/patient/year	-	11.74 [d]	11.70 [e]
Cost/patient/year	-	$[redacted] [f]	$[redacted] [f]
Proportion of patients on treatment	12 months: 94% [g]	12 months: 60% [h] 24 months: 47% [h] 36 months: 36% [h] 48 months: 28% [h] 60 months: 22% [h]	Not estimable [i]

Source: Table 6 of the VALIANT 52-week trial report; Table 2-8, p49 of the submission; Section 3 economic model Excel workbook; Section 4 financial implications Excel workbook

Abbreviations: DPMQ, dispensed price for maximum quantity; UPCR, urine protein-creatinine ratio

[a] Based on an assumed 89.74%/10.26% public/private hospital split

[b] Trial-based compliance in both treatment arms during the overall study period (total number of infusions divided by total expected number of infusions)

[c] Assumption

[d] Based on 90% adherence multiplied by 13.04 scripts per year

[e] Based on 90% adherence multiplied by 13.00 scripts per year

[f] Cost per 28 days multiplied by scripts per patient per year

[g] Based on total number of patients discontinuing treatment during the overall study period (4/63 patients, 6.3%)

[h] Proportion of patients on treatment at the start of each year. Based on assumed treatment discontinuations per 3-month cycle of 5% in better UPCR health states (UPCR<1, UPCR 1-3) and 80% in the worse UPCR health state (UPCR>3), and assuming all patients discontinue treatment when switching to dialysis

[i] Due to the prevalence-based approach used to derive the financial estimates (which did not explicitly model pegcetacoplan initiations and discontinuations among treated patients), the numbers of patients initiating and continuing treatment in each year could not be determined. In each year, 4 months of initial treatment (13 scripts per year × 4/12 = 4.33 scripts) and 8 months of continuing treatment adjusted for the proportion achieving a clinical benefit (80%) and treatment persistence (90%; 13 scripts per year × 8/12 × 0.80 × 0.90 = 6.24 scripts) were assumed for the proportion of the eligible population on treatment.

6.90 The submission did not include any administration costs associated with pegcetacoplan in the economic analyses (economic model and cost-minimisation framework) or financial estimates. This may not be reasonable given the submission claimed that in the Australian setting, patients are likely to receive pegcetacoplan subcutaneous infusions either through hospital day units or supported home infusion.

6.91 The submission did not include additional costs associated with vaccines and vaccine administration. This was inappropriate given mandatory vaccinations against encapsulated bacteria including meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) as per the draft product information and in the proposed restriction.

6.92 The submission assumed that the use of pegcetacoplan would not be associated with increased diagnostic and monitoring costs. It is unclear whether this assumption was reasonable given additional treatment-related monitoring requirements for kidney function and proteinuria (as per the proposed restriction) as well as monitoring for infections and adverse events associated with complement inhibition.

Estimated PBS usage & financial implications

6.93 This submission was jointly considered by DUSC and ESC. The submission used a prevalence-based epidemiological approach to estimate the utilisation and financial implications of listing pegcetacoplan for the treatment of patients aged ≥12 years with C3G or primary IC-MPGN. The prevalence-based approach used to derive the financial estimates did not explicitly model pegcetacoplan initiations and discontinuations among treated patients. As a result, the underlying numbers of patients initiating and continuing treatment in each year of the financial estimates could not be determined. The pre-PBAC response stated that the submission used a prevalent approach whereby annual cohorts were considered separately, to avoid double counting with an annual incident population. This meant that initiations and discontinuations were considered within the eligible population uptake and eligibility criteria.

6.94 Table 16 presents the key inputs relied on in the financial estimates.

Table 16: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Australian population aged ≥12 years	2026: 23,962,489 2027: 24,347,849 2028: 24,723,857 2029: 25,079,076 2030: 25,415,004 2031: 25,736,468	Population projections, Australia (2023; ABS 3222.0 Series B data).	This is reasonable.
Prevalence of C3G	20.5 per million	The PSCR clarified that the assumed C3G prevalence of 20.5 per million was obtained from a systematic literature review including 11 studies reporting prevalent or incident cases of IC-MPGN or C3G. The pooled estimate was adjusted for mortality using an adjustment factor of 0.714. The estimated C3G prevalence was applied to the forecast annual Australian population aged ≥12 years.	No Australian C3G prevalence estimates were identified. The assumptions and methodology used to calculate the prevalence rates were not provided. It is unclear whether the pooled prevalence rate derived from the meta-analysis reflects the prevalence of C3G in Australia. The Sub-Committees commented that the age range of patients included in these studies was unclear and it was unclear whether applying the estimates only to the Australian population aged ≥12 years was appropriate. The reported cases in the literature may have included some patients with secondary disease, whereas the proposed restriction specifies patients with primary C3G.

Data	Value	Source	Comment
			There was inadequate documentation and the methodology used to derive the mortality adjustment factor could not be verified. The PSCR provided additional detail with regards to the mortality adjustment. The Sub-Committees considered that application of a mortality adjustment appeared reasonable, but considered that it was still unclear how this was calculated.
Prevalence of IC-MPGN	16.2 per million	The PSCR clarified that the assumed IC-MPGN prevalence of 16.2 per million was obtained from a systematic literature review including 11 studies reporting prevalent or incident cases of IC-MPGN or C3G. The pooled estimate was adjusted for mortality using an adjustment factor of 0.714. The estimated IC-MPGN prevalence was applied to the forecast annual Australian population aged ≥12 years.	No Australian IC-MPGN prevalence estimates were identified. The assumptions and methodology used to calculate the prevalence rates for each of the included studies were not provided, and it is unclear whether the included studies reflect the prevalence of IC-MPGN in Australia. The reported cases in the literature may have included some patients with secondary disease, whereas the proposed restriction specifies patients with primary IC-MPGN. There was inadequate documentation of the methodology used to derive the mortality adjustment factor. The Sub-Committees commented that the age range of patients included in these studies was unclear and therefore it was unclear whether applying the estimates only to the Australian population aged ≥12 years was appropriate. The PSCR provided additional detail with regards to the mortality adjustment. The Sub-Committees considered that application of a mortality adjustment appeared reasonable but considered that it was still unclear how this was calculated.
Diagnosis rate (C3G and IC-MPGN)	Yr 1-2: 52.50% Yr 3-4: 63.75% Yr 5-6: 71.25%	Assumption; the submission argued that the proportion of patients who are diagnosed would increase over time due to improvements in clinical awareness, biopsy access, and complement testing.	The adjustment of the prevalent population to account for the diagnosis rate was not appropriate, as the prevalence estimates would already reflect the rates of diagnosis for C3G and IC-MPGN. Higher disease detection rates due to clinical awareness, biopsy access, and complement testing would result in an increase in the underlying disease prevalence rates.

Data	Value	Source	Comment
			The Sub-Committees agreed with the commentary and considered this parameter should be removed from the financial estimates.
Proportion with subclinical disease (C3G and IC-MPGN)	15%	Assumption; the submission argued that patients with subclinical disease are unlikely to present with symptoms and would only be diagnosed incidentally. The 15% adjustment was applied to the assumed diagnosis rate.	This assumption did not appear reasonable given that patients with subclinical disease are unlikely to undergo a renal biopsy, which is required for diagnosis of C3G and IC-MPGN, and the proportion of patients that are managed with standard care alone would already be accounted for in the assumed pegcetacoplan uptake rates. The proposed restriction does not include any requirements relating to disease severity (e.g., a minimum level of proteinuria). The Sub-Committees agreed with the commentary and considered this parameter should be removed from the financial estimates.
Proportion not in Stage 5 CKD (C3G and IC-MPGN)	60%	The submission stated that the proportion was derived from Sinha (2025). Sinha (2025) conducted a cross-sectional survey of nephrologists actively managing C3G (N=195) and their patients (N=385) in France, Germany, Italy, Spain, the UK, the US, China, and Japan, conducted in 2023.	The underlying source of the estimate applied was unclear. In the Sinha publication, 8.3% of patients were reported to be receiving dialysis, 13.7% were reported to have an eGFR of 15-29 mL/min/1.73 m^2, and 6.7% were reported to have an eGFR of <15 mL/min/1.73 m^2 at the time of completing the survey (i.e. 20.4% were stage 4 or 5 CKD). A proportion of patients with Stage 5 CKD will receive a kidney transplant and may subsequently become eligible for treatment pegcetacoplan. If treatment with pegcetacoplan results in stabilisation of renal function (and an associated delay in progression to dialysis), a higher proportion of patients will remain eligible for continuing treatment with pegcetacoplan over time.

Data	Value	Source	Comment
			The Sub-Committees considered it uncertain how this parameter (60%) was derived. The Sub-Committees noted the proposed restriction excludes initiation of patients with eGFR<30 mL/min/1.73 m^2 i.e. Stages 4 or 5 CKD, while the financial estimates only exclude patients with Stage 5 CKD. The Sub-Committees noted in Sinha 2025, 20.4% of patients were reported with Stage 4 or 5 CKD, which would also include patients receiving dialysis. The Sub-Committees considered this parameter be revised to 79.6%. Additionally, the Sub-Committees considered this eligible population may decrease if a criterion for proteinuria was included in the restriction.
Grandfathered patients	[redacted][1] patients	The submission estimated that up to [redacted][1] patients will be receiving pegcetacoplan for C3G and IC-MPGN through clinical trials or compassionate access at the time of PBS listing. Grandfathered patients were assumed to be accounted for in the prevalent patient estimates.	This appears reasonable.
Treatment utilisation			
Uptake rate (C3G and IC-MPGN)	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Assumption; the submission argued that the proportion of treated patients is expected to increase over time, with growing clinical experience and broader recognition of complement-mediated disease, and as clinicians become more confident in initiating treatment earlier in the disease course.	The uptake rates were difficult to interpret due to the prevalence-based approach used to derive the financial estimates. While the uptake of pegcetacoplan is considered uncertain, it is likely to be higher than estimated in the initial years of listing given there are no other complement inhibitors listed on the PBS for the treatment of C3G or IC-MPGN. The PSCR argued, "the uptake rate assumptions are intended to reflect nephrologist experience and initial uncertainty related to clinician adoption." The Sub-Committees agreed with the commentary that uptake rates are likely to be underestimated and considered uptake rates be revised to 80% in Years 1 and 2 and 90% in Years 3-6.
Proportion continuing treatment (C3G and IC-MPGN)	80%	Assumption; based on the proposed continuing treatment restriction criteria and clinician feedback. In each treatment year, all patients were assumed to receive 4 months of initial treatment with pegcetacoplan, and 80% of patients were assumed to receive 8 months of continuing treatment.	While the proposed restriction requires patients to have experienced a clinical improvement as a result of treatment with pegcetacoplan, no objective response measures are included, and it is unclear how this criterion will be interpreted in clinical practice.

Data	Value	Source	Comment
			Due to the prevalence-based approach used to derive the financial estimates, it is unclear whether the implementation of this assumption in the budget impact model was reasonable as it applies to all patients in each year of the estimates.
Treatment persistence	90%	Assumption; an additional adjustment for treatment persistence was applied to the duration of continuing treatment in each treatment year (90% × 8 months continuing treatment = 7.2 months).	Due to the prevalence-based approach used to derive the financial estimates, it is unclear whether the implementation of this assumption in the budget impact model was reasonable.
Treatment adherence	90%	Assumption; the submission argued that treatment adherence for pegcetacoplan is expected to be consistent with real-world experience in chronic rare disease therapies requiring regular administration.	No references to support the assumed treatment adherence rate were provided.
Costs			
Pegcetacoplan	$[redacted]	Proposed effective DPMQ (8 × 1,080 mg vials).	-
Public/private hospital split	89.74%/10.26%	Based on dispensing data for PBS Items 13175K, 13180Q, 13185Y, 13191G, 13196M, 13197N (pegcetacoplan for the treatment of PNH) in calendar year 2024.	In the absence of specific dispensing data for medicines used to treat CG3 and IC-MPGN, this appears reasonable.
Patient copayment	$19.46 per PBS script	Average PBS and RPBS copayments based on dispensing data for PBS Items 13175K, 13180Q, 13185Y, 13191G, 13196M, 13197N (pegcetacoplan for the treatment of PNH) in calendar year 2024.	In the absence of specific dispensing data for medicines used to treat CG3 and IC-MPGN, this appears reasonable. All pegcetacoplan scripts dispensed for PNH were PBS scripts.

Source: Section 4, pp105-119 of the submission; Section 4 financial implications Excel workbook
Abbreviations: C3G, C3 glomerulopathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex mediated membranoproliferative glomerulonephritis; UK, United Kingdom; US, United States; Yr, Year
The redacted values correspond to the following ranges:
[1] *< 500*

6.95 Table 17 presents the estimated use and financial implications of listing pegcetacoplan on the PBS/RPBS for the treatment of C3G and primary IC-MPGN.

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [b]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of pegcetacoplan						
Net cost to the PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][7]	$[redacted][7]
Net cost to MBS	$0	$0	$0	$0	$0	$0
Net cost to the PBS/RPBS/MBS	**$[redacted][3]**	**$[redacted][4]**	**$[redacted][5]**	**$[redacted][6]**	**$[redacted][7]**	**$[redacted][7]**

Source: Section 4 financial implications Excel workbook.

[a] Estimated by multiplying the number of eligible patients in each year by the assumed uptake rate. The numbers of patients initiating and continuing treatment with pegcetacoplan in each year of listing were not explicitly modelled.

[b] In each year, 4 months of initial treatment (13 scripts per year × 4/12 = 4.33 scripts) and 8 months of continuing treatment (with adjustments applied for the proportion achieving a clinical benefit and persistence; 13 scripts per year × 8/12 × 0.80 × 0.90 = 6.24 scripts) were assumed. The number of scripts was further adjusted for treatment adherence of 90%.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

[5] *$30 million to < $40 million*

[6] *$40 million to < $50 million*

[7] *$60 million to < $70 million*

6.96 The estimated cost of pegcetacoplan to the PBS/RPBS was $0 to < $10 million in Year 1, increasing to $60 million to < $70 million in Year 6, a total cost of $200 million to < $300 million over the first 6 years of listing.

6.97 The cost to the PBS/RPBS is considered highly uncertain and likely underestimated for the following reasons:

- The prevalence-based approach used to derive the financial estimates did not explicitly model pegcetacoplan initiations and discontinuations among treated patients. As a result, the underlying numbers of patients initiating and continuing treatment in each year of the financial estimates could not be determined, and it is unclear whether the implementation of the uptake rates, treatment persistence, and the proportion of patients achieving a clinical benefit with pegcetacoplan in the budget impact model were reasonable. The Sub-Committees considered a prevalence based approach would be appropriate in a population that has reached a steady state (where the number of treated patients remains approximately constant over time) and with stable treatment duration (average duration of treatment– from initiation, discontinuation, progression, transplant or death, remains stable over time). The Sub-Committees considered neither of these assumptions would hold if pegcetacoplan delays progression or reduces mortality. The Sub-Committees considered a combined prevalence and incidence approach would be more appropriate to capture initiation and continuation of treatment.
- The prevalence of C3G and primary IC-MPGN in Australia are unclear. There was a substantial variation in the prevalence rates derived from international studies reporting cases of C3G and IC-MPGN. The assumptions and methodology used to calculate the prevalence rates for each of the included studies were not provided and there was inadequate documentation of the methodology used to derive the

mortality adjustment factor. The pre-PBAC response acknowledged that the Australian incidence and prevalence of C3G and primary IC-MPGN is uncertain due to their rarity, differing and evolving case definitions and biopsy practices and underdiagnosis.

- The adjustment of the prevalent patient numbers to account for the C3G and IC-MPGN diagnosis rates was not appropriate, as the prevalence estimates would already capture the rates of diagnosis for C3G and IC-MPGN.
- The adjustment of the prevalent population to account for patients with subclinical disease did not appear reasonable, given that patients with subclinical disease are unlikely to undergo a renal biopsy, which is required for diagnosis of C3G and IC-MPGN. The proportion of patients who are managed in early stages of the disease with standard care alone would already be accounted for in the assumed pegcetacoplan uptake rates.
- The submission assumed that 40% of patients would be ineligible for treatment with pegcetacoplan due to having Stage 5 CKD. In the publication cited as the source for this estimate (Sinha 2025), at the time of the survey completion, 13.7% were reported to have an eGFR of 15-29 mL/min/1.73 m^2, and 6.7% were reported to have an eGFR of <15 mL/min/1.73 m^2. The Sub-Committees noted the proposed restriction excludes patients with Stage 4 or 5 CKD and as such, based on Sinha 2025, the proportion of patients ineligible due to having Stage 4 or 5 CKD to be 20.4% (13.7% + 6.7%).
- A proportion of patients with Stage 5 CKD will receive a kidney transplant and may subsequently be eligible for treatment with pegcetacoplan, however these patients were not explicitly included in the estimates.
- Uptake rates were considered uncertain and likely to be underestimated in the initial years of listing, given that there are no other complement inhibitors listed on the PBS for the treatment of C3G or IC-MPGN.
- There is potential for use outside of the proposed restriction among patients who do not achieve a clinical benefit during the initial treatment period, or patients with an eGFR <30m mL/min/1.73 m^2 at the time of treatment initiation. The Sub-Committees considered the ongoing use in patients not achieving clinical benefit or in patients with eGFR <30m mL/min/1.73 m^2 was small.

6.98 The evaluation noted that the financial estimates were sensitive to the prevalence of C3G and IC-MPGN, the diagnosis rate, the proportion with subclinical disease, the proportion who are not in Stage 5 CKD, the treatment uptake rates, the proportion continuing treatment and the treatment adherence.

Quality Use of Medicines

6.99 The submission did not identify any quality use of medicines issues, and no activities to support the quality use of medicines were proposed.

6.100 The Sub-Committees noted the Product Information contains a boxed warning relating to serious infections caused by encapsulated bacteria and the requirement to vaccinate and/or revaccinate according to current national vaccination guidelines.

6.101 The Sub-Committees noted prescribing information in the restriction (both initial and continuing) states: "Prior to prescribing this drug, the prescriber must contact the pharmaceutical company to confirm that the patient has received all relevant vaccinations. The prescriber will then be provided with a Controlled Distribution Reference Number (CDRN) and information about the pumps and consumables for use." The Sub-Committees commented that the sponsor did not provide details regarding how these vaccination records would be obtained. Additionally, the Sub-Committees noted the submission did not account for the cost of immunisations in the financial estimates, however noted the financial impact would be low relative to the cost of pegcetacoplan.

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

7 PBAC Outcome

7.1 The PBAC did not recommend listing pegcetacoplan for treatment of complement 3 glomerulopathy (C3G) or primary immune complex membranoproliferative glomerulonephritis (IC-MPGN). The PBAC considered that there is a high clinical need for treatments for C3G or IC-MPGN, which are conditions that impact relatively young patients and cause decline in kidney function. The PBAC noted the clinical benefit was only supported by evidence of changes in surrogate measures, with a statistically significant reduction in proteinuria and evidence of a slower decline in eGFR compared to placebo. The PBAC considered that, on the basis of these differences, it is possible that pegcetacoplan provides a clinical benefit for some patients in terms of slowing progression to end-stage kidney disease. The PBAC considered that the modelled benefits relating to avoiding long-term dialysis and transplant were improbable and highly uncertain due to the limited clinical data, reliance on indirect measures of health benefit, and unsupported assumptions. The PBAC considered that there was a high level of uncertainty in the modelled costs and outcomes and the very high ICERs reflect the high price requested for pegcetacoplan. The PBAC advised that a substantial price reduction would be required for pegcetacoplan to be considered cost-effective.

7.2 The PBAC considered that the primary reason for this outcome was the economic evaluation.

7.3 The PBAC acknowledged that C3G is a disease which predominantly affects adolescents and young adults and the impacts of this disease included severely disrupting education, employment, family life and mental health. Input from individuals, healthcare professionals and organisations had a strong emphasis on the importance of early and equitable access to effective treatment for CG3. The PBAC

considered that there is a high clinical need for treatments for C3G, noting that other treatments are limited to supportive measures which do not impact the underlying mechanism of C3G, and most patients progress to end-stage kidney disease (requiring dialysis or transplant) despite these therapies. The inputs noted that reducing the incidence of kidney failure can prevent physical, mental and emotional symptoms, prevent reduced quality of life and life participation as well as reduce carer burden and loss of income for patients and their families and carers. The inputs also noted that pegcetacoplan is well tolerated and acceptable to patients despite the requirement for subcutaneous administration. The PBAC valued the inputs provided as they allowed additional insight into the patient, carer and health care provider perspective for a rare disease.

7.4 The PBAC considered that the proposed clinical place was appropriate. The proposed clinical place for pegcetacoplan was as initial treatment in patients with native kidneys who have moderate to severe disease, in addition to supportive measures with ACEI/ARB, SGLT2 inhibitors, as well as blood pressure control. The submission also suggested that for patients with native kidneys use of pegcetacoplan would result in reduced use of immunosuppressive therapy in clinical practice. The PBAC considered this was reasonable, although the majority of patients in the VALIANT trial continued to receive immunosuppressant therapy. The PBAC also noted that a small number of patients in the VALIANT trial had received a kidney transplant. The PBAC considered that treatment of patients with C3G or primary IC-MPGN recurrence following a kidney transplant was clinically appropriate given the same mechanism of disease and noting the high clinical need for disease modifying treatments for these patients.

7.5 The PBAC considered that the proposed restrictions were generally appropriate and aligned with the population in the clinical evidence (VALIANT trial). The PBAC considered that a Written Authority level would be appropriate for the initial and grandfather restrictions and Telephone/Online Authority level would be appropriate for the continuing listings. The PBAC considered that it would not be appropriate to limit treatment to patients with decreased serum C3 levels as it is uncertain whether C3 levels are a treatment effect modifier. The PBAC considered that the following additional changes to the restrictions would be appropriate:

- Additional eligibility criteria for post-transplant patients should be revised such that eligibility requires biopsy-proven disease recurrence.
- Addition of a criterion requiring patients to have proteinuria ≥1.0 g/day under the initial treatment restriction, consistent with the trial population.
- Addition of a treatment criterion requiring continued use of supportive measures as appropriate (optimised use of ACEI/ARB +/- SGLT2), consistent with clinical guidelines and the with trial population.
- The first continuing restriction should specify that patients must demonstrate evidence of improvement or stabilisation of disease defined as a ≥50% reduction in FMU UPCR or a ≤15% decrease in eGFR from baseline after 16

weeks of treatment. For subsequent continuing restrictions demonstration of improvement or stabilisation of disease based on clinician judgement would be appropriate, given the progressive nature of C3G and primary IC-MPGN.

7.6 The PBAC considered the nominated main comparator of "standard of care" (supportive measures that include renin-angiotensin system inhibition with ACEI/ARB, SGLT2 inhibitors and blood pressure control; as well as general immunosuppression e.g. mycophenolate mofetil, corticosteroids) was appropriate, and noted that iptacopan is also a relevant near-market comparator.

7.7 The submission's comparison with standard of care was based on a head-to-head randomised trial of pegcetacoplan versus placebo in patients with C3G or primary IC-MPGN (VALIANT) over a 26-week double blind period followed by a 26-week open label period. The primary outcome from VALIANT was change in first morning UPCR with key secondary outcomes of change in eGFR and the composite endpoint (≤15% reduction in eGFR and ≥50% reduction in UPCR). The PBAC noted the outcomes in the key trial reflected short-term changes in proteinuria and eGFR, with comparative data limited to 6 months. The submission presented epidemiological evidence supporting the use of reduction in proteinuria and stabilisation in eGFR as surrogate measures for the target clinical outcome of end stage kidney disease, however there were no direct data demonstrating that treatment-related changes in proteinuria or eGFR would result in a quantifiable change in the risk of kidney failure specifically in patients with C3G/primary IC-MPGN. The PBAC considered that biological plausibility and epidemiological evidence support proteinuria and eGFR levels as well-established prognostic variables for kidney disease progression, and this was supported by the clinician in the sponsor hearing. However, the magnitude by which proteinuria reduction or eGFR stabilisation mitigates progression to ESKD and its associated sequelae remains uncertain. The PBAC agreed with the Sub-Committees that it would be difficult to attain data to demonstrate treatment-related changes in proteinuria or eGFR that result in a quantifiable change in the risk of kidney failure in these patients.

7.8 The PBAC noted that treatment with pegcetacoplan was associated with a statistically significant reduction in first morning UPCR compared to placebo at 26 weeks, and effects on proteinuria were sustained at 12 months during the open-label extension period. However, the PBAC noted that although there was a numerical difference in the decline in eGFR between the treatment arms the value was not formally tested for statistical significance due to the hierarchical endpoint testing strategy and the PBAC considered that the duration of the double-blind phase of the trial was likely too short and the sample size too small to unequivocally demonstrate any reduction in eGFR decline. The PBAC also noted that the eGFR decline in the placebo arm was substantially faster than would be expected in clinical practice, which added uncertainty in interpreting this outcome. The PBAC also noted that the comparative period of the trial was likely too short to demonstrate differences in quality of life measures. Overall, the PBAC considered that the claim of superior comparative effectiveness over standard of care was adequately supported by the data for the

surrogate measure of reduction in proteinuria, for which there is strong biologically plausibility for an impact on kidney disease, however, the magnitude of change in eGFR was less certain.

7.9 The PBAC noted that pegcetacoplan was associated with a higher rate of infections/infestations and infusion site related AEs compared with placebo. The PBAC noted that adverse events of special interest included an increased risk of the incidence of infections (serious/severe or caused by encapsulated bacteria) compared to placebo. The PBAC considered the claim of non-inferior safety was not reasonable and a claim of inferior comparative safety would be appropriate. The PBAC noted that the draft product information for pegcetacoplan 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, with recommendations to vaccinate against these bacteria prior to initiation of pegcetacoplan treatment. The PBAC advised it would be appropriate to extend access to these vaccines on the National Immunisation Program (NIP) for a person who is undergoing treatment, or will commence treatment with pegcetacoplan for a condition specified under the Pharmaceutical Benefits Scheme (PBS).

7.10 The submission also presented a Bucher indirect comparison of pegcetacoplan (VALIANT) versus iptacopan (APPEAR-C3G) using placebo as a common reference. Although the VALIANT and APPEAR-C3G trials shared similar trial designs and outcome definitions, the VALIANT trial population was broader as it included adolescents, primary IC-MPGN, post-transplant recurrent disease, patients with serum C3 levels above 77 mg/dL (0.85 × lower limit of normal) and did not exclude those with signs of rapidly progressive crescentic glomerulonephritis. Baseline 24-hour UPCR levels were similar between trials, however eGFR levels suggested that the APPEAR-C3G population could be at an earlier stage of disease, with better preserved kidney function compared to those in the VALIANT trial. In addition, the eGFR decline in the placebo arm of VALIANT that was substantially faster than the placebo arm of the APPEAR-C3G trial of iptacopan suggested that there were meaningful differences between the populations included in the VALIANT and APPEAR-C3G trials. The indirect comparison suggested that pegcetacoplan was associated with statistically significantly greater relative reductions in UPCR compared to iptacopan, but this was uncertain due to these transitivity issues. There was no apparent difference between pegcetacoplan and iptacopan in terms of mean change in eGFR from baseline. The PBAC considered that the claim of superiority over iptacopan was not adequately supported by the data due to key differences between the VALIANT and APPEAR-C3G trial populations in the indirect comparison.

7.11 The submission presented a cost-utility analysis for the economic evaluation of pegcetacoplan compared to standard of care. The PBAC noted the model was complex, and that there were limited trial data to model disease progression. The treatment benefit beyond the indirect measures over the 26 week duration of the comparative phase of the trial and most of the data inputs informing the model, relied

on post hoc analyses or were drawn from sources that were not adequately justified in the submission. The PBAC noted that the evaluation and the Sub-Committees considered the cost-effectiveness estimate should not be considered reliable given uncertainties with modelled change in eGFR estimates based on the VALIANT trial that were substantially worse than in other studies of C3G/IC-MPGN, the assumption that all post-transplant patients (with a successful graft) have immediate disease recurrence which substantially underestimates the effectiveness of transplantation, inadequately justified dialysis utility values and limitations with the model structure that precluded the ability to explore the impact of differences in patient and disease characteristics.

7.12 Based on the economic model, treatment with pegcetacoplan was associated with an incremental cost per QALY gained of $755,000 to < $855,000 compared to SoC for the treatment of C3G or primary IC-MPGN. A multivariate sensitivity analysis using mean EQ-5D-3L utility values from Cooper (2020) and removing UPCR disutilities for all CKD stages increased the ICER to > $1,055,000 per QALY gained. The PBAC considered that in addition to the high level of uncertainty in the modelled costs and outcomes, the very high ICERs from the submission model reflect the high price requested for pegcetacoplan and advised that a substantial price reduction would be required for pegcetacoplan to be considered cost-effective. The PBAC recalled that the same advice had been provided regarding the submission for iptacopan for C3G (paragraph 7.16, iptacopan Public Summary Document [PSD], November 2025 PBAC meeting).

7.13 The PBAC also recalled its advice regarding the submission for iptacopan for C3G from the November 2025 meeting that, although there are limited trial data for iptacopan, modelling disease progression and treatment benefit in patients with C3G was feasible and could provide confidence in the cost-effectiveness of iptacopan with a more conservative approach to modelling the treatment benefit for C3G (paragraph 7.16, iptacopan PSD, November 2025 PBAC meeting). The PBAC acknowledged that there were challenges in estimating the long-term benefits from complement inhibitors (iptacopan and pegcetacoplan) for patients with the rare conditions of C3G and primary IC-MPGN based on the small trials, with short comparative treatment phases. On balance, the PBAC considered that, given the data to inform economic models for iptacopan and pegcetacoplan are limited, the uncertainty in the ICER was unlikely to be adequately resolved with further revision to the economic models. In the context of a substantial price reduction, and noting the clinical need and available evidence, the PBAC considered the cost-effectiveness may be able to be assessed using a cost/responder approach. The PBAC considered that a cost per responder approach should provide interpretation, and quantification where possible, of the clinically meaningful benefits that are expected to result from reduced proteinuria and potential reduction in decline in eGFR response, for example, avoiding or delaying dialysis and transplants.

7.14 The submission used a prevalence-based approach used to derive the financial estimates, which did not explicitly model pegcetacoplan initiations and

discontinuations among treated patients. As a result, the underlying numbers of patients initiating and continuing treatment in each year of the financial estimates could not be determined and it was unclear whether the uptake rates, treatment persistence, and the proportion of patients achieving a clinical benefit with pegcetacoplan in each year were reasonable. The PBAC agreed with the Sub-Committees that a combined prevalence and incidence approach would be more appropriate to capture initiation and continuation of treatment. The PBAC considered that the prevalence of C3G and primary IC-MPGN were uncertain as no reliable Australian sources were available but the values applied by the submission appeared reasonable. The PBAC considered that the adjustments of the prevalent patient numbers to account for diagnosis rates and patients with subclinical disease were not reasonable as prevalence rates would already account for these factors. The PBAC considered that the proportion of patients assumed to be ineligible due to stage 5 CKD was uncertain and should be revised as advised by the Sub-Committees (see Table 16), and that the proportion of patients who require treatment following a kidney transplant should also be explicitly considered.

7.15 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.

- Revisions to the proposed listing (see paragraph 7.5)
- A substantial reduction in the cost of pegcetacoplan (see paragraph 7.12).
- A simplified cost-effectiveness analysis including cost per responder analyses with interpretation of the ratio(s) provided (see paragraph 7.13).
- Revised financial estimates (see paragraph 7.14).
- Proposal of an risk sharing agreement (RSA) to address the risk of use in a much larger population than expected, or for longer than expected and in the context of highly uncertain cost-effectiveness for pegcetacoplan.

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.

7.16 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.