6.04 IPTACOPAN, Capsule 200 mg, Fabhalta®, NOVARTIS PHARMACEUTICALS AUSTRALIA PTY LIMITED.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 85, Authority Required (Written) listing for iptacopan for the treatment of adults with complement 3 glomerulopathy (C3G) with either native kidneys or disease recurrence following a kidney transplant.

1.2 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	Adults aged ≥18 years with C3G with native kidneys or disease recurrence following a kidney transplant
Intervention	Iptacopan 200 mg orally twice a day
Comparator	Standard of care
Outcomes	Reduction in proteinuria and improvements in eGFR leading to delay/avoidance of end stage kidney disease, and related improvements in survival and quality of life. Increase in treatment-related adverse events.
Clinical claim	Iptacopan is superior in terms of efficacy and inferior in terms of safety compared to standard of care

Source: Table 1.1, p4 of the submission
Abbreviations: C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC parallel process. The TGA Delegate's Overview was available for the November 2025 PBAC meeting.

2.2 The proposed indication for iptacopan was for the treatment of adult patients with C3G. The TGA Delegate's Overview stated that the indication wording may require further restrictions or conditions and requested ACM advice regarding whether the indication should include all subtypes or be more restrictive or targeted to specific conditions.

2.3 Iptacopan is FDA-approved for the treatment of adults with C3G to reduce proteinuria and it is EMA-approved for the treatment of adult patients with C3G in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated.

2.4 Iptacopan is currently approved by the TGA for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH). Iptacopan was recommended by PBAC for PNH in July 2024 and listed in the PBS on 1 November 2025.

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

3 Requested listing

3.1 The proposed listing with changes suggested by the Secretariat is shown below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IPTACOPAN					
~~I~~ *i*ptacopan 200 mg capsule, 56	Published: $[redacted] Effective: $[redacted]	1	56	5	Fabhalta

Concept ID	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners
	Benefit type: ☒ Authority Required in writing only via OPA/post/HPOS upload)
	Prescribing rule level:
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
33720	**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* ~~A~~ applications for authority to prescribe ~~should~~ *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
29959	**Caution:** This drug increases the risk of encapsulated bacterial infections. Consult the approved Product Information for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection.
	Restriction Summary [new1] / Treatment of Concept: [new1A]
	Episodicity: [blank]
	Severity: [blank]
	Condition: Complement 3 glomerulopathy (C3G)
New I1	**Indication:** Complement 3 glomerulopathy (C3G)
	Treatment Phase: Initial treatment – *native kidney patients* ~~(new patient)~~
New CC	**Clinical criteria:**
New CC	~~Patient must have a diagnosis of C3G, confirmed by kidney biopsy, prior to initiating treatment with this drug~~ *Patient must have/have had a confirmed diagnosis of complement 3 glomerulopathy (C3G) evidenced by kidney biopsy prior to commencing treatment with this drug*

	AND
New CC	**Clinical criteria:**
New CC	~~Patient must have an estimated glomerular filtration rate of at least 30 mL/min/1.73 m2 prior to initiating treatment with this drug~~ *Patient must have/have had an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2 prior to commencing treatment with this drug*
	AND
New CC	**Clinical criteria:**
New CC	~~Patient must have a urine protein-creatine ratio (UPCR) of at least 1.0 g/g or 113 mg/mmol prior to initiating treatment with this drug~~ *Patient must have/have had a urine protein-creatine ratio (UPCR) of at least 1.0 g/g (or 113 mg/mmol) prior to commencing treatment with this drug*
	AND
New CC	**Clinical criteria:**
New CC	~~Patient must have been stabilised on an ACE inhibitor or Angiotensin II receptor antagonist to receive treatment with this drug unless such treatment is medically contraindicated or cannot be tolerated~~ *Patient must have been stabilised on either: (i) ACE inhibitor, (ii) Angiotensin II receptor antagonist (ARB), prior to commencing treatment with this drug, unless intolerant/contraindicated according to the TGA-approved Product Information*
	AND
23150	***Clinical criteria:***
22518	*Patient must not have had a kidney transplant*
New TC	**Treatment criteria:**
13590	Must be treated by a nephrologist; or
New TC	Must be treated by a non-specialist medical physician or nurse practitioner who has consulted a nephrologist on the patient's drug treatment details
27771	**Population criteria:**
27770	~~Patient must be 18 years of age or older~~ *Patient must be at least 18 years of age.*
	~~**AND**~~
~~New PC~~	~~***Population criteria:***~~
~~New PC~~	~~Patient must not have had a kidney transplant~~
34070	**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).
New PI	***Prescribing Instructions:*** *At the time of authority application, details of the following must be provided:* *(a) eGFR and UPCR at baseline* *(b) Details (date, unique identifying number/code or provider number) of the pathology report confirming C3G diagnosis via kidney biopsy* *(c) Treatment with ACE inhibitor or Angiotensin II receptor antagonist (ARB) dose and duration* *All results and reports must be documented in the patient's medical records.*
	Restriction Summary [new2] / Treatment of Concept: [new2A]
	Episodicity: [blank]
	Severity: [blank]

	Condition: Complement 3 glomerulopathy (C3G)
New I1	**Indication:** Complement 3 glomerulopathy (C3G)
	Treatment Phase: Initial treatment – *post-transplant patients* ~~(new patient)~~
New CC	**Clinical criteria:**
New CC	~~Patient must have a diagnosis of recurrent C3G following a kidney transplant, confirmed by kidney biopsy, prior to initiating treatment with this drug~~ *Patient must have/have had a confirmed diagnosis of complement 3 glomerulopathy (C3G) evidenced by kidney biopsy prior to commencing treatment with this drug*
	AND
New CC	***Clinical criteria:***
New CC	*The condition must be recurrent following a kidney transplant*
	AND
New CC	***Clinical criteria:***
New CC	*Patient must have/have had an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2 prior to commencing treatment with this drug*
	AND
New CC	***Clinical criteria:***
New CC	*Patient must have/have had normal or elevated urinary protein excretion prior to commencing treatment with this drug.*
New TC	**Treatment criteria:**
13590	Must be treated by a nephrologist; or
New TC	Must be treated by a non-specialist medical physician or nurse practitioner who has consulted a nephrologist on the patient's drug treatment details
27771	**Population criteria:**
27770	~~Patient must be 18 years of age or older~~ *Patient must be at least 18 years of age.*
34070	**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).
New PI	***Prescribing Instructions:*** *At the time of authority application, details of the following must be provided:* *(a) eGFR and UPCR at baseline* *(b) Details (date, unique identifying number/code or provider number) of the pathology report confirming C3G diagnosis via kidney biopsy* *All results and reports must be documented in the patient's medical records.*

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
IPTACOPAN					
↳ *i*ptacopan 200 mg capsule, 56	NEW	1	56	5	Fabhalta

Concept ID	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners
	Benefit type: ☒ Authority Required (Streamlined) [new code]
	Prescribing rule level:
7606	***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.*

7607	***Administrative Advice:*** *No increase in the maximum number of repeats may be authorised.*
29959	***Caution:*** *This drug increases the risk of encapsulated bacterial infections.* *Consult the approved Product Information for information about vaccination against meningococcal, pneumococcal and Haemophilus influenzae type B (Hib) infection.*
	Restriction Summary [new3] / Treatment of Concept: [new3A]
	Episodicity: [blank]
	Severity: [blank]
	Condition: Complement 3 glomerulopathy (C3G)
New I1	**Indication:** Complement 3 glomerulopathy (C3G)
	Treatment Phase: Continuing treatment
24642	**Clinical criteria:**
24641	Patient must have received PBS-subsidised treatment with this drug for this condition
	AND
29976	**Clinical criteria:**
29975	Patient must have experienced clinical improvement as a result of treatment with this drug; or
30003	Patient must have experienced *a* stabilisation of the condition as a result of treatment with this drug.
	AND
29346	**Clinical criteria:**
29345	Patient must discontinue treatment with this drug prior to initiating renal replacement therapy, defined as dialysis or kidney transplantation
New TC	**Treatment criteria:**
13590	Must be treated by a nephrologist; or
New TC	Must be treated by a non-specialist medical physician or nurse practitioner who has consulted a nephrologist on the patient's drug treatment details
27771	**Population criteria:**
27770	~~Patient must be 18 years of age or older~~ *Patient must be at least 18 years of age.*
~~New PI~~	~~**Prescribing Instructions:**~~ ~~The authority application must be made in writing and must include:~~ ~~(1) details of the proposed prescription; 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).~~

3.2 The essential elements and requested restrictions in the submission were based on 30-day dispensing. However, the submission requested consideration of 60-day dispensing for iptacopan given its ease of administration and simple storage requirements as an oral therapy. The submission claimed that 60-day dispensing would also improve treatment compliance and reduce logistical burden on patients and their caregivers. Treatment costs in the economic model and financial estimates were based on 30-day dispensing only.

3.3 The sponsor proposed a special pricing arrangement for iptacopan. The submission requested the same published prices for C3G as proposed for PNH but stated that different indication-specific effective prices were requested.

3.4 The proposed restriction for patients with native kidneys was narrower than the proposed TGA indication as it also requires a minimum level of kidney function,

elevated proteinuria, and concomitant treatment with ACEI/ARB unless intolerant or contraindicated.

3.5 The submission requested that the PBAC consider extending the restriction to include adolescents aged 12 to 17 years. The submission acknowledged, however, that the efficacy and safety of iptacopan in this population is currently being investigated in the ongoing APPEAR-C3G trial with expected completion in 2026. The requested expanded population would be broader than the currently proposed TGA indication (adults). The sponsor's Australian advisory board claimed that the age criterion would likely not exclude too many patients as only a relatively small proportion of patients present in adolescence or earlier.

3.6 The proposed restriction for patients with native kidneys was broader than the key trial population that excluded patients with rapidly progressive crescentic glomerulonephritis (RPGN), those with > 50% interstitial fibrosis/tubular atrophy (IF/TA), or presence of monoclonal gammopathy of undetermined significance (MGUS), a pre-malignant haematological condition. Patients with these conditions typically have worse prognosis and may follow different treatment pathways. It was unclear whether treatment with iptacopan should be allowed in these patients given the lack of data.

3.7 The submission proposed the PBS population should include post-transplant patients with disease recurrence, however the risk-benefit profile and cost-effectiveness of iptacopan for this indication is uncertain, with no comparative data in this group of patients. The Pre-Sub-Committee Response (PSCR) noted that inclusion of post-transplant patients was based on the high unmet clinical need. The PSCR also noted C3G impacts native and transplanted kidneys in the same way, and iptacopan has the same mechanism of action in both patient groups. The proposed restriction for post-transplant patients was broad, with no clinical criteria other than confirmation of C3G recurrence by kidney biopsy. Supportive evidence provided in the submission was based on a narrower population who had a minimum eGFR of ≥30 mL/min/1.73 m^2 and had to be on a stable dose of immunosuppressants for at least 3 months prior to treatment with iptacopan.

3.8 The proposed continuing restriction states that patients must have clinical improvement or stabilisation of the condition in order to continue treatment with iptacopan. The sponsor's advisory board indicated that reduction in proteinuria and improvements in eGFR would constitute clinical improvement but should have numerical values included if specified in the restriction. However, it was also noted that if the intent is to keep the criteria broad then the terminology could be left as written.

3.9 The proposed restriction also requires discontinuation of treatment with iptacopan prior to patients commencing kidney replacement therapy, defined as dialysis or kidney transplantation. The draft product information notes that there are no data available in patients with severe kidney impairment or on dialysis and no dose recommendations were provided.

3.10 The treatment criteria allow for initial, continuing and grandfathering scripts to be prescribed by nephrologists and non-specialist medical physicians or nurse practitioners who have consulted with a nephrologist. This was inconsistent with the sponsor's advisory board that indicated that treatment initiation would require specialist nephrology care, both for accurate diagnosis and ongoing monitoring. It was unclear whether it is appropriate for iptacopan to be prescribed by non-specialist medical physicians or nurse practitioners given the rarity and complexity of this condition.

3.11 The submission requested grandfathering provisions for patients treated with iptacopan prior to PBS listing for C3G in patients with native kidneys and post-transplant patients. The submission stated there are currently < 500 patients with C3G who are receiving treatment with iptacopan. However, with the amended wording in the initial restrictions, separate grandfathering provisions would not be necessary.

3.12 The draft product information for iptacopan included 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 iptacopan treatment.

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

4 Population and disease

4.1 C3G is a rare form of glomerulonephritis, where there is inflammation in the kidney. The condition is characterised by dysregulation of the alternative complement pathway that is part of the immune system, resulting in a build-up of C3 proteins in the kidneys which lead to inflammation and structural damage.

4.2 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 (swelling in some areas of the body) and reduced urine output. Patients with C3G have variable degrees of kidney function impairment at presentation and variable rates of kidney function decline.

4.3 The diagnosis of C3G is established by kidney biopsy based on characteristic findings on immunofluorescence microscopy. C3G is further divided into two subtypes, C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) based on findings using electron microscopy. Additional testing for monoclonal gammopathy, serum complement proteins, autoantibodies and genetic testing are then used to identify the underlying cause of the glomerulopathy.

4.4 Rates of progression vary widely in reports of C3G, with some patients having persistently low-grade proteinuria but maintaining kidney function for a long time while other patients have severe nephrotic syndrome, and some can present with

rapidly progressive glomerulonephritis and have a poor prognosis. There is no consensus between published studies as to whether the prognosis of C3GN and DDD are different or comparable (UpToDate – C3 glomerulopathies: DDD and C3G, July 2025). 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.

4.5 There are limited epidemiological data available for C3G in Australia. The sponsor's advisory board stated that there was poor data capture due to the lack of standardised coding for C3G with no systematic approach for case identification and tracking. Anecdotally, patients tend to present young (in their 20s or 30s) and are often diagnosed late (or incidentally) due to misdiagnosis, with true diagnosis established only after multiple biopsies. The advisory board claimed that lack of awareness of the disease, lack of standardised pathways and limited access to resource-intensive diagnostic tests were barriers to timely referral and specialist care.

4.6 Global epidemiological studies report an incidence of 1 to 3 cases per million and point prevalence of 14 to 140 cases per million (Smith 2019). Patients are typically diagnosed between 20 and 30 years of age, although the proportion of children and adolescents aged less than 18 years can vary from 24 to 61% (Caravaca-Fontán 2023, Masoud 2024 pre-print).

4.7 The submission claimed that there is a clinical need for effective, safe and tolerable treatments for C3G, as current treatment options are limited to supportive measures including renin-angiotensin inhibition with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) with or without immunosuppressive therapies.

4.8 There is no formal guidance for the treatment of C3G. The Kidney Disease Improving Global Outcomes (KDIGO) 2021 guidelines encourage the use of supportive measures to manage complications associated with glomerular disease such as controlling oedema, reducing proteinuria and managing blood pressure. Treatments include renin-angiotensin inhibition with ACEI/ARB and/or diuretics. Additional conservative measures include statin therapy to control cholesterol and low-density lipoprotein levels. The KDIGO 2021 guidelines also recommend initial treatment with immunosuppressants (mycophenolate mofetil and glucocorticoids) in patients with moderate to severe disease (defined as proteinuria ≥1 g/day and haematuria or declining kidney function for at least 6 months).

4.9 More recent guidelines for treatment of C3G were identified during the evaluation (UpToDate July 2025 – C3 glomerulopathies: Dense deposit disease and C3 glomerulonephritis). Treatment recommendations in UpToDate were largely consistent with the KDIGO 2021 guidelines. However, UpToDate uses a proteinuria threshold of 1.5 g/day to differentiate between mild and moderate to severe disease while the KDIGO guidelines used 1 g/day. The UpToDate authors noted that the nominated threshold was arbitrary and based on clinical experience, claiming there is no evidence to support a specific proteinuria threshold in patients with C3G.

4.10 The UpToDate guidelines also suggest different treatment options according to disease severity: supportive measures only in patients with mild disease and the addition of immunosuppressants in patients with moderate to severe disease and escalating measures of immunosuppression in patients with rapidly progressive disease (intravenous pulse glucocorticoids, cyclophosphamide, mycophenolate mofetil).

4.11 The KDIGO and UpToDate guidelines indicate that patients who fail immunosuppressant therapy should consider treatment with eculizumab. Eculizumab is neither TGA-approved nor PBS-listed for treatment of C3G.

4.12 Patients who experience kidney failure should be considered for dialysis or kidney transplant. However, disease recurrence and graft loss are common in patients following a kidney transplant as standard immunosuppression may not correct the underlying abnormality. Limited guidance is available for the treatment of patients with disease recurrence following a kidney transplant. The ESC noted that public consultation input from consumers and consumer organisations indicated that the delay or avoidance of dialysis and kidney transplant were important to patients and that access to these treatments were a challenge to patients in regional areas.

4.13 Iptacopan is a proximal complement inhibitor that targets Factor B, to selectively inhibit the alternative complement pathway. It is presumed that the therapeutic effects of iptacopan are due to prevention of the downstream build-up of C3 protein in the kidneys. The ESC noted that public consultation input from healthcare providers and medical organisations indicated that a targeted therapy, addressing the root cause of the disease (over-production of C3 and deposition in the glomeruli) would be expected to benefit patients significantly.

4.14 Iptacopan is intended as chronic treatment for C3G and discontinuation is not recommended unless clinically indicated. The sponsor's advisory board noted that treatment would likely be long-term or until significant clinical progression. However, it was noted that there is a lack of data on optimal duration of therapy, safety monitoring and discontinuation in real-world practice.

4.15 In patients with native kidneys, the submission positioned iptacopan as an add-on to background therapy with an ACEI/ARB, with or without corticosteroids and/or mycophenolate mofetil.

4.16 In patients with disease recurrence following a kidney transplant, the submission positioned iptacopan as an add-on to standard immunosuppressive regimens.

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. The main argument provided in support of this nomination was that there are no therapies currently listed on the PBS for the treatment of C3G.

5.2 In patients with native kidneys, standard of care was defined as supportive measures that include renin-angiotensin inhibition with ACEI/ARB, in addition to immunosuppressants (mycophenolate mofetil and glucocorticoids) where clinically appropriate. In post-transplant patients with disease recurrence, standard of care includes adjustment of the post-transplant immunosuppression regimen. The ESC agreed with the evaluation that standard of care is an appropriate main comparator.

5.3 The submission identified pegcetacoplan as a near-market comparator. Pegcetacoplan is a complement 3 inhibitor currently under TGA evaluation for treatment, in adults and adolescents (aged 12-17 years), of kidney diseases C3G and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN).

5.4 The submission noted that the key trial of pegcetacoplan, VALIANT (NCT05067127), was completed in June 2025. The submission claimed that limited published data were available at the time of submission and that further information would be required to determine the feasibility of an indirect comparison of iptacopan and pegcetacoplan in the requested populations. VALIANT was a phase 3, randomised, placebo-controlled trial in adults and adolescents with C3G or IC-MPGN. A full trial publication was not available during the evaluation. Top-line results suggested that pegcetacoplan was associated with a 68% reduction in proteinuria compared to placebo at Week 26, which was sustained at one year. The ESC noted that this outcome appeared to be more favourable for pegcetacoplan than for iptacopan (68% versus 35% reduction in proteinuria compared to placebo at Week 26, see Table 4). However, potential differences in the trial and included populations have not been assessed.

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 noted that in the past there have been no effective treatments and discussed the limitations of available treatments. The clinician noted that C3G was associated with poor outcomes, with deterioration often over a short period of time, and that the patients likely to progress quickly to ESKD are those with high levels of protein in their urine. The clinician noted that iptacopan is well-tolerated and clinicians are comfortable managing safety aspects as it is used in other indications.

6.2 The clinician commented on the outcome of proteinuria in the trial, as being a key marker for management in kidney disease and for determining who is likely to experience more rapid loss of kidney function. The clinician noted the potential impact of iptacopan on slowing the rate of progression to ESKD and noted that in other indications, like IgA nephropathy, reducing proteinuria results in better outcomes , supporting its use as a surrogate endpoint. The clinician noted that younger patients have to lose a lot of kidney function for there to be a demonstrable change in eGFR

though histological changes are occurring in terms of scarring, and predictors of scarring include proteinuria.

6.3 The clinician noted that patients who receive transplants often recur and sometimes are not considered for another transplant and so remain on dialysis. The clinician noted that the hope that access to therapy can change the outcome for patients who receive transplants and would otherwise recur. The clinician noted there were small numbers in patients with kidney transplant in the clinical trials but considered that they are likely to benefit from iptacopan.

6.4 The PBAC considered the clinician statements were informative, however, the Committee did not consider the submission had adequately supported reduction in proteinuria as a surrogate marker of longer-term kidney function.

Consumer comments

6.5 The PBAC noted and welcomed the input from individuals (2), health care professionals (14) and organisations (4) via the Office of Health Technology Assessment Consultation Hub. The inputs from health professionals described C3G as rare and complex to diagnose, with most individuals (50%) experiencing progression to ESKF within 10 years of diagnosis, and high rates of recurrence after kidney transplant (60-90%). Input highlighted the unmet need for effective therapies to treat the underlying pathophysiology of C3G and described iptacopan's benefits as: potential increased effectiveness compared to current treatments; reduced immunosuppressive side-effects; reduced morbidity and excess mortality associated with dialysis; reduced healthcare costs associated with dialysis; reduced demand for donor organs for transplant; and extending transplant survival in patients with recurrent C3G. Input noted clinical trial evidence suggests iptacopan is well tolerated, noting the need to manage increased risk of infection but that this is a well-known and manageable risk. Input described the impact of symptom burden on individuals who are often children or young adults, working, and raising or starting families. Input highlighted symptoms of end-stage kidney disease including fatigue, itch, poor appetite and oedema, requiring individuals to frequently interact with the healthcare system, impacting their ability to attend school and work and causing significant carer burden. The input from individuals with C3G noted the impact of chronic kidney disease, relapses and treatment burden on their ability to participate in daily activities and their mental health.

6.6 The PBAC noted and welcomed the advice received from specialist organisations (the Transplantation Society of Australia and New Zealand Ltd (TSANZ), Australian and New Zealand Society of Nephrology), and consumer representative groups (Kidney Health Australia and Transplant Australia Ltd) in support of PBS listing of iptacopan. Input from specialist organisations indicated patients often experience significant delays in diagnosis (which requires specialist nephrology services and diagnostic procedures). In addition, input noted that optimal treatment strategies for C3G using currently available therapies have not been established, but that an international consensus

statement will shortly recommend complement inhibition as first-line therapy for C3G. Input from consumer groups highlighted the toll of dialysis and transplantation on patients, families and their support systems, and on the healthcare system, and the difficulty of accessing dialysis for patients in rural and remote areas. Input also noted the loss of graft function due to recurrent C3G can have a profound emotional impact on donors and their and families.

Clinical studies

6.7 The submission was based on a head-to-head randomised trial of iptacopan versus placebo in patients with C3G who have native kidneys (APPEAR-C3G). Outcomes were based on the May 2024 data cut for the completed adult cohort. The trial was ongoing for the adolescent cohort with expected completion in July 2026.

6.8 The following studies were included as supportive evidence: a phase 2, non-randomised study of iptacopan in adult patients with C3G who have native kidneys or recurrent C3G following a kidney transplant (X2202); and a long-term extension study of iptacopan (B12001B) in the subset of patients who rolled over from the APPEAR-C3G trial and the X2202 phase 2 study.

6.9 Details of the included studies are provided in Table 2. The ESC noted that an additional publication reporting on the APPEAR C3G study was available at the time of ESC consideration (Kavanagh (2025)).

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
APPEAR-C3G (CLNP023B12301)	Novartis (2024). A multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of iptacopan (LNP023) in complement 3 glomerulopathy	Internal study report
	Nester et al (2025). Efficacy and safety of iptacopan in patients with C3 glomerulopathy: 12-month results from the phase 3 APPEAR-C3G study	*Kidney International Reports* 10(2): S136-S137
	Novartis (2024). SCE Appendix 2: C3 glomerulopathy, High-level efficacy summary for adult patients who completed APPEAR-C3G and rolled over into Study B12001B	Internal study report
	Kavanagh (2025) Oral iptacopan therapy in patients with C3 glomerulopathy: a randomised, double-blind, parallel group, multicentre, placebo-controlled, phase 3 study.	*The Lancet. September 25, 2025*
X2202 (CLNP023X2202)	Novartis (2022). An open-label, non-randomized study on efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of LNP023 in two patient populations with C3 glomerulopathy	Internal study report
	Wong et al (2023). Efficacy and safety of iptacopan in patients with C3 glomerulopathy	*Kidney International Reports* 8:2754-2764
	Nester et al (2025). Iptacopan reduces proteinuria and stabilizes kidney function in C3 glomerulopathy	*Kidney International Reports* 10:432-446
B12001B (CLNP023B12001B)	Novartis (2024). An open-label, non-randomized extension study to evaluate the long-term efficacy, safety and tolerability of iptacopan (LNP023) in C3 glomerulopathy or idiopathic immune-complex membranoproliferative glomerulonephritis (36-months interim analysis of participants from Study CLNP023X2202)	Internal study report
Pooled analysis (APPEAR-C3G, X2202, B12001B)	Novartis (2025). CTD 2.5 Clinical overview in C3 glomerulopathy	Internal study report
	Novartis (2025). CTD 2.7.3 Summary of clinical efficacy in C3 glomerulopathy	Internal study report
	Novartis (2025). 2.7.4 Summary of clinical safety in C3 glomerulopathy	Internal study report

Source: Table 2.5, p57 of the submission

6.10 The key features of the included studies are summarised in Table 3.

Table 3: Key features of the included studies

Study	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
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)	High	Adults with biopsy-proven C3G who have native kidneys, eGFR ≥30 mL/min/1.73 m^2, UPCR ≥1.0 g/g and reduced serum C3 (< 0.85 LLN). On maximally recommended/tolerated dose of ACEI/ARB and stable doses of other antiproteinuric medications [a]	Primary: change in UPCR Other: eGFR, achievement of a composite renal endpoint (proteinuria reduction ≥50% and eGFR change ≤15%), disease activity score, quality of life (FACIT-Fatigue, SF-36, EQ-5D-5L)	Baseline characteristics

Study	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Iptacopan single-arm studies						
X2202	Cohort A (native kidneys), N=16 Cohort B (post-transplant), N=11	Phase 2, open-label, two cohort, single-arm study (3-month run-in, 12-week treatment period and optional 12-week extension)	High	Cohort A Adults with biopsy-proven C3G who have native kidneys, eGFR ≥30 mL/min/1.73 m^2, FMV UPCR ≥100 mg/mmol (or ≥1 g/24h total urinary protein excretion) and reduced serum C3 (< 0.90 LLN). On maximally recommended/ tolerated dose of ACEI/ARB and stable doses of other antiproteinuric medications [a] Cohort B Adults with biopsy-proven C3G recurrence after kidney transplantation, eGFR ≥30 mL/min/1.73 m^2 and normal/elevated urinary protein excretion. On stable doses of immunosuppression with no evidence of allograft rejection	Cohort A Primary: change in UPCR Other: change in other biomarkers of kidney function including eGFR Cohort B Primary: change in C3 Deposit Score Other: change in other biomarkers of kidney function including eGFR	Not used
B12001B	Rollover from X2202, N=26 Rollover from APPEAR-C3G, N=66	Open-label, non-randomised extension study (planned data collection up to 66 months for patients from X2202) [b]	High	Patients who completed study X2202 or the APPEAR-C3G trial	Achievement of composite renal endpoints [c], change in kidney function biomarkers (UPCR, eGFR)	Not used
Pooled analysis						
APPEAR-C3G, X2202, B12001B	90	Exploratory analysis including historical data	High	Patients in the APPEAR-C3G trial, X2202 study (native kidneys cohort) and B12001B extension study	Annualised eGFR slope (mL/min/1.73 m^2 per year)	Rate of eGFR decline in the placebo arm

Source: Section 2.3, pp59-71; Section 2.4, pp72-99 of the submission

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; FMV, first morning void; LLN, lower limit of normal; UPCR, urine protein-creatinine ratio

[a] Including mycophenolate mofetil/sodium, corticosteroids (up to 7.5 mg per day), SGLT2 inhibitors and mineralocorticoid receptor antagonists

[b] Primarily designed as an extension to study X2202 but also allows for optional transition of patients completing two other trials of iptacopan for C3G (APPEAR-C3G) and IC-MPGN (APPARENT)

[c] Assessed in the X2202 rollover population only: 2-component renal endpoint (≤15% reduction in eGFR and ≥50% reduction in UPCR) and 3-component renal endpoint (≤10% reduction in eGFR and either a 50% reduction in UPCR or a reduction to UPCR < 300 mg/g

6.11 The risk of bias in the APPEAR-C3G trial was minimised by the randomised controlled study design and blinding. However, there were notable imbalances between treatment arms at baseline in terms of key parameters of disease severity (age at diagnosis, proteinuria level, eGFR level) and subtype (C3GN versus DDD). The study report noted that these imbalances were consistent with patients randomised to

iptacopan presenting with a more severe disease phenotype. These differences introduce a potentially high risk of bias in terms of study results.

6.12 The applicability of the APPEAR-C3G population to the proposed PBS population is uncertain given the lack of Australian patient characteristics. During the evaluation, patient characteristics based on medical history at diagnosis from the APPEAR-C3G trial were compared with data from the UK National Registry of Rare Kidney Diseases (RaDaR) registry and the Spanish Group for the Study of Glomerular Disease (GLOSEN) registry, used to inform alternative inputs in the economic model.

6.13 The APPEAR-C3G trial and observational study cohorts differed in terms of patient demographics, disease phenotype, clinical presentation and kidney function at diagnosis. At diagnosis, more than half the APPEAR-C3G population were adults while the RaDaR population were predominantly paediatric and the majority of patients in the GLOSEN registry were adults. The registry cohorts had substantially lower eGFR levels and worse clinical presentation at diagnosis compared to the key trial, therefore representing different baseline risks of disease progression. The evaluation considered the risk profile of the APPEAR-C3G trial population was not well-characterised in the submission. The PSCR noted that the criteria in the proposed PBS restriction (biopsy-confirmed C3G, proteinuria ≥1 g/g, and eGFR ≥30 mL/min/1.73m^2) are consistent with the population enrolled in the APPEAR-C3G trial, and background therapies were consistent with Australian clinical practice. The PSCR also argued that subgroup analyses from APPEAR-C3G showed consistent efficacy across age, sex, race, and baseline disease severity, supporting generalisability of the trial data to the Australian context. The ESC noted that there was a high level of variation in characteristics across the three cohorts (APPEAR-C3G, RaDaR and GLOSEN) and considered the APPEAR-C3G population is likely to be reasonably representative of the Australian PBS population.

6.14 The submission noted that X2202 and B12001B were non-randomised, open-label studies which inherently carry a high risk of bias due to potential confounding, lack of blinding and potential selection bias.

6.15 An exploratory analysis of the rate of change in eGFR (slope per year) was conducted by pooling data from the APPEAR-C3G, X2202 and B12001B studies (but using the native kidney cohort of X2202 only) including historical estimates collected for approximately 2 years prior to entry into APPEAR-C3G and X2202. The historical data were combined with screening/run-in values to calculate the rate of change in eGFR (slope) prior to treatment initiation. Data from the placebo arm during the 6-month double-blind period of APPEAR-C3G were also included in the historical, pre-treatment period. The post-iptacopan treatment period included data from the 6-month double-blind and 6-month open-label period in APPEAR-C3G (patients randomised to iptacopan and patients randomised to placebo who switched to iptacopan during the open-label period), patients treated with iptacopan for 3 months in the X2202 phase 2 study and patients who rolled over to the B12001B extension study, with total exposure to iptacopan of up to 4.75 years.

6.16 The clinical overview in the C3G study report noted heterogeneity in terms of study populations and study designs including study duration and primary endpoints across the included studies (APPEAR-C3G, X2202 and B12001B). The risk of bias for the pooled analysis is high due to the uncontrolled nature of the exploratory analysis that did not account for heterogeneity across the included studies. There is also potential for confounding, with substantial differences in the use of supportive treatments in the key trial population (26% versus 99% on ACEI/ARB in the pre- and post-randomisation periods, respectively) and methodological limitations such as pooling of data from non-parallel observation periods which would affect the reliability of results from the analysis. The ESC noted that Kavanagh (2025) also presented an exploratory analysis of the rate of change in eGFR for the APPEAR-C3G trial only, which would address the heterogeneity across studies, but not the potential for confounding or methodological limitations as in the analysis that included all three studies (e.g. pooling of historical data and the double-blind period of placebo arm in the pre-iptacopan phase; pooling of data from the double-blind and open-label periods of the iptacopan arm, and open-label crossover period of the placebo arm in the post-iptacopan phase).

6.17 Outcomes in the key trial and supportive studies were primarily based on short-term changes in proteinuria and eGFR. 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.

6.18 There is a biologically plausible link between proteinuria and eGFR with kidney disease progression and the epidemiological evidence generally supports the use of these biomarkers as prognostic variables. However, the data were mainly derived from observational or retrospective studies that are prone to incorrect or incomplete diagnosis classification, data collection and capture of outcomes. The sponsor's C3G natural history report also noted considerable heterogeneity in treatment approaches and analytic methods across the observational studies and potential risk of misclassification of diagnosis due to the relatively recent introduction of C3G specific diagnostic codes (from 2019 onwards).

6.19 Overall, the evaluation considered it is unclear whether proteinuria reduction or stabilisation in eGFR are surrogate measures for the target clinical outcome of delay or avoidance of end-stage kidney disease as there are no 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.

6.20 A review of C3G trial endpoints by an expert panel was identified during the evaluation (Developing therapies for C3G, Report of the Kidney Health Initiative C3G Trial Endpoints Work Group; Nester 2024). The panel noted that favourable treatment effects on proteinuria, eGFR and histopathology would provide convincing evidence of treatment efficacy that targeted the complement pathway; and that a therapy might be considered effective in the absence of complete alignment of all 3 endpoints if there was meaningful lowering of proteinuria and stabilisation or improvement in

eGFR. However, the panel was unable to define a minimum threshold for change in any of the endpoints that might be considered clinically meaningful.

6.21 The ESC noted that Nester (2024) showed that registry data suggested that:

- Reductions in proteinuria of > 50% or to very low levels was associated with a lower hazard of kidney failure, however this was based on retrospective and observational data and findings were inconsistent across cohorts.
- eGFR decline was a robust predictor of kidney failure, with a slower eGFR decline over 24 months associated with a lower hazard of kidney failure. However, the ESC noted that the APPEAR-C3G trial only captured 6 months of comparative data and outcomes can be confounded by drug-related haemodynamic effects or changes in serum creatinine.

6.22 Overall, the ESC considered there is biological plausibility and epidemiological evidence supporting proteinuria and eGFR levels as prognostic variables for kidney disease progression. However, the magnitude by which proteinuria reduction or eGFR stabilisation mitigates progression to ESKD and its associated sequelae remains uncertain. The pre-PBAC response reiterated that proteinuria is a validated surrogate marker in glomerular diseases and strongly predictive of long-term renal outcomes. The sponsor referred to:

- a retrospective cohort analysis of patients with C3G using longitudinal registry UK data (RaDaR, N=203), Masoud et al (2025), which demonstrated that decline in UPCR is significantly associated with reduced risk of kidney failure.
- a multicentre, retrospective study of 149 patients with C3G (N=98) or IC-MPGN (N=51), Caravaca-Fontán et al. (2025) which determined that a 30% reduction in proteinuria at 6 months was associated with a significantly slower decline in eGFR, similar to those seen in healthy individual, and a lower risk of kidney failure.

Comparative effectiveness

APPEAR-C3G trial

6.23 Table 4 presents results for the primary endpoint of change in urinary protein-creatinine ratio (UPCR) at 6 months in the APPEAR-C3G trial.

Table 4: Change in 24-hour urinary protein-creatinine ratio (UPCR, g/g) at 6 months

Treatment arm	Baseline, Geo-mean (95% CI)	Month 6, Geo-mean (95% CI)	Ratio to baseline (95% CI) [a]	Treatment difference, % reduction (95% CI) [a]
Iptacopan N = 38	3.33 (2.79, 3.97)	2.17 (1.62, 2.91)	0.70 (0.57, 0.85)	**35.1 (13.8, 51.1)**
Placebo N = 36	2.58 (2.18, 3.05)	2.80 (2.37, 3.30)	1.08 (0.88, 1.31)	

Source: Table 2.27, p99 of the resubmission; Table 14.2-1.3a, p310 of the APPEAR-C3G trial report
Abbreviations: CI, confidence interval; Geo-mean, geometric mean
[a] Based on a mixed model with repeated measures analysis of log-transformed geometric mean UPCR ratio to baseline

6.24 Treatment with iptacopan was associated with a statistically significant reduction in 24-hour UPCR compared to placebo at 6 months from baseline. Sensitivity analyses using alternative imputation approaches following intercurrent events (changes to therapy that can affect proteinuria levels) produced results that were consistent with the primary analysis. *Post hoc* sensitivity analyses were also performed, adjusting for

imbalances in several baseline characteristics between arms including eGFR, age and C3G subtype. The results were consistent with the primary analysis.

6.25 Treatment effects on proteinuria were sustained at 12 months during the open-label extension period and up to 24 months in the B12001B long-term extension study.

6.26 A *post hoc* analysis was conducted to evaluate the proportion of patients with different levels of proteinuria during the trial. In the iptacopan arm, the proportion of patients with nephrotic range proteinuria (defined as UPCR ≥3 g/g) reduced from 55.3% at baseline to 31.6% and 36.8% at 6 and 12 months, respectively. The proportion of patients in the placebo arm with nephrotic range proteinuria increased from 30.6% at baseline to 41.7% at 6 months; and decreased to 27.8% after switching to open-label iptacopan treatment for 6 months.

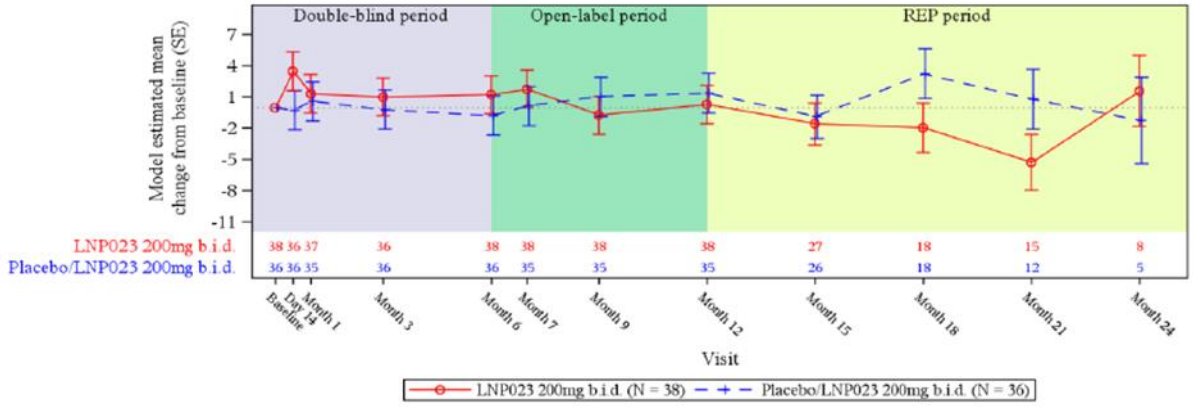
6.27 Table 5 presents results for the secondary endpoint of change in eGFR at 6 months in the APPEAR-C3G trial and Figure 1 presents changes in eGFR in the APPEAR-C3Gtrial and B12002B extension study.

Table 5: Change in eGFR (mL/min/1.73 m²) at 6 months

Treatment arm	Baseline, Mean (SD)	Month 6, Mean (SD)	Adjusted mean change (95% CI) [a]	Treatment difference (95% CI) [a]
Iptacopan N = 38	89.3 (35.2)	90.5 (38.2)	1.30 (-2.14, 4.73)	2.16 (-2.75, 7.06)
Placebo N = 36	99.2 (26.9)	98.5 (27.6)	-0.86 (-4.36, 2.64)	

Source: Table 2.30, p105 of the submission; Table 14.2-3.4, p386 of the APPEAR-C3G trial report
Abbreviations: CI, confidence interval; SD, standard deviation
[a] Based on a mixed model of repeated measures analysis which included treatment, visit, and stratification variable as fixed effects, treatment×visits as interaction term and baseline eGFR as covariate

Figure 1: Plot of mean change in eGFR over time in the APPEAR-C3G trial and B12001B long term extension study



Source: Figure 3-2, p10 of the 2.7.3 Appendix 2 - summary of clinical efficacy report of the submission
Abbreviations: b.i.d., twice a day; eGFR, estimated glomerular filtration rate; LNP023, iptacopan; REP, rollover extension program; SE, standard error
Note: Analysed using a mixed model repeated measures analysis which included treatment, visit, stratification variable as fixed effects, treatment×visit as an interaction term and baseline eGFR as a covariate. Correlations between visits within patients were modelled using an autoregressive covariance matrix

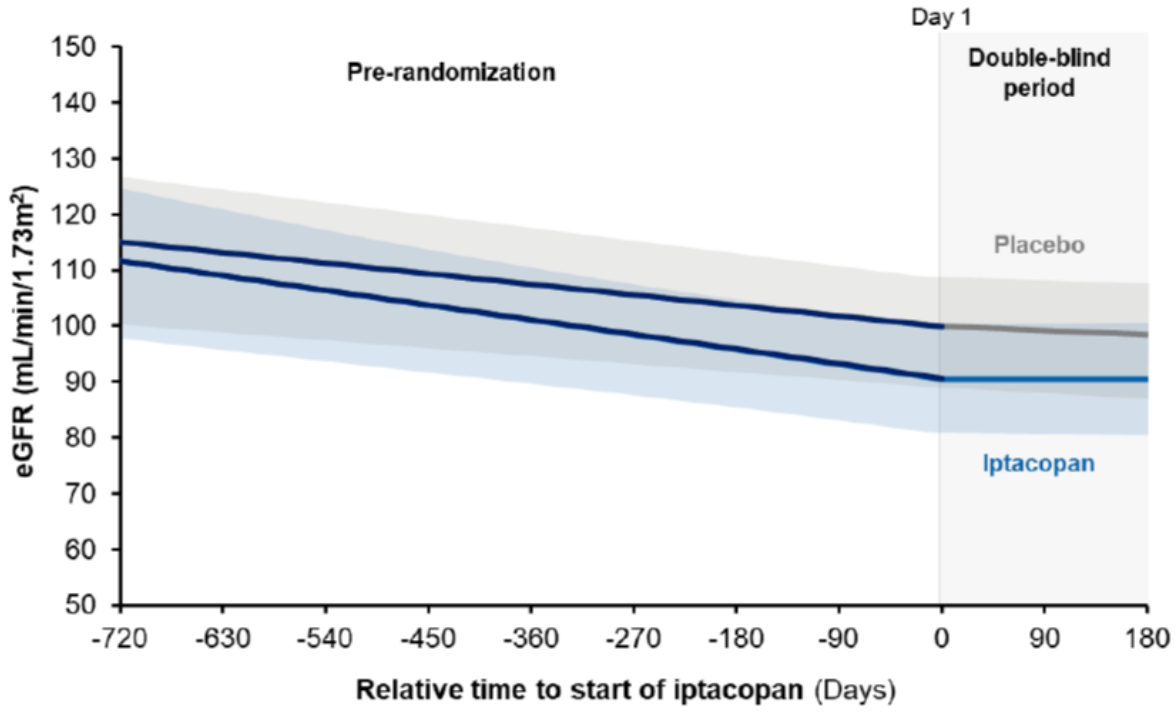
6.28 Treatment with iptacopan was associated with a numerical improvement in eGFR compared to placebo at 6 months, however, the result did not achieve statistical significance. The eGFR slope (mL/min/1.73 m^2 per year) was estimated as -0.03

(95% CI -6.93, 6.88) in the iptacopan arm and -3.08 (95% CI -10.13, 3.98) in the placebo arm with a non-statistically significant difference of 3.05 (95% -6.82, 12.92) between arms. Longer-term follow-up showed a decline in eGFR at 21 months in patients originally randomised to the iptacopan arm of the trial (-5.2 mL/min/1.73 m^2 from baseline). The study report stated that it was likely a transient effect due to variability in eGFR, with the result reflecting a combination of the small number of observations at that timepoint (n=15) and the impact of outlier values. In patients originally randomised to placebo and subsequently switched to iptacopan, eGFR remained fairly stable throughout the trial and extension period.

6.29 The trial report noted significant variability in change in eGFR between arms across subgroups in the pre-specified subgroup analysis, with point estimates favouring the placebo arm compared to iptacopan depending on region, corticosteroid and/or mycophenolate mofetil use at baseline, baseline eGFR and age at diagnosis. The report noted that interpretation of the results was difficult and there was additional uncertainty given the small sample size of the study. It was unclear whether there are any potential treatment effect modifiers in terms of change in eGFR.

6.30 The ESC noted that the Kavanagh (2025) publication presented results of a post hoc analysis of change in eGFR slope by individual treatment arms. The results of this analysis are presented in Figure 2.

Figure 2 Post hoc analysis of change in eGFR slope by individual treatment arm in APPEAR-C3G



	eGFR slope (mL/min/1.73m²/year)		
	Iptacopan	Placebo	Iptacopan vs placebo
Pre-randomization	**-10.75** (-15.51, -6.00)	**-7.64** (-12.28, -3.00)	
Double-blind period	**-0.03** (-6.93, 6.88)	**-3.08** (-10.13, 3.97)	**3.05** (-6.82, 12.92)
Difference pre-vs double-blind	**10.73** (3.23, 18.23)	**4.56** (-2.90, 12.02)	**6.17** (-4.41, 16.74)

Source: Figure S9, p31 of the Kavanagh 2025 appendix
Abbreviation: eGFR, estimated glomerular filtration rate
Note: Generalised linear mixed model was used to predict change in eGFR over time, with an intercept, treatment group effect, a pre-treatment slope, a change in the slope at visit Day 1 as fixed effects, random effects on intercept, the pre-treatment slope and change in slope, interaction between treatment group and pre-treatment slope and interaction between treatment group and a change in the slope. Intercurrent events handled with a treatment policy strategy

6.31 The analysis showed that the annualised eGFR slope during the historical period was worse in the iptacopan arm (-10.75 mL/min/1.73 m2 per year) compared to the placebo arm (-7.64 mL/min/1.73 m2 per year). However, both arms showed stabilisation/slowed decline in eGFR slope during the double-blind period of the trial. The difference in change in eGFR slope between treatment arms was in favour of iptacopan although it was not statistically significant (6.17 mL/min/1.73 m2 per year, 95% CI -4.41, 16.74).

6.32 The Kavanagh (2025) study authors noted that the stabilisation/slowed decline of eGFR slope during the double-blind period could be a result of more frequent monitoring and better adherence to supportive treatment including RAAS inhibitors and background immunosuppression within the structured trial environment. This suggests that observed differences during the double-blind period are a more robust representation of treatment effects associated with iptacopan rather than observational comparisons of 'before and after' iptacopan treatment.

6.33 Table 6 presents results based on the secondary composite renal endpoint consisting of a ≤15% decrease in eGFR and a ≥50% reduction in UPCR at 6 months compared to baseline.

Table 6: Composite renal endpoint (≤15% decrease in eGFR and a ≥50% reduction in 24-hour UPCR) at 6 months

Outcome	Iptacopan N = 38	Placebo N = 36	Odds ratio (95% CI)
Composite renal endpoint, n/N (%)	11/37 (29.7)	2/36 (5.6)	**7.15 (1.43, 35.72)**
- ≤15% decrease in eGFR	34/38 (89.5)	32/36 (88.9)	
- ≥50% reduction in UPCR	11/37 (29.7)	2/36 (5.6)	

Source: Table 2.40, p115 of the resubmission

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; UPCR, urine protein-creatine ratio

Note: Initiation of any complement pathway modifying agent or initiation/intensification of corticosteroid or immunosuppressant therapy, or renal replacement therapy was designated as the patient not having met the endpoint

6.34 Results for the composite renal endpoint were statistically significant based on the multiple testing procedure, in favour of iptacopan compared to placebo. The difference between arms was driven by the proportion of patients achieving ≥50% reduction in 24-hour UPCR at 6 months. Results at 12 months during the open-label extension period were supportive of sustained treatment effects with iptacopan.

6.35 Supplementary analyses based on a lower threshold of change in eGFR (≤10% reduction) produced results that were consistent with the primary analysis (odds ratio 6.18, 95% CI 1.23, 31.0). Change in UPCR was also evaluated using lower percentage reduction thresholds. In the iptacopan arm, 67.6%, 45.9% and 43.2% of patients had UPCR decreases of ≥20%, ≥30% and ≥40%, respectively, whereas these thresholds were achieved by only 19.4%, 11.1% and 11.1% of patients, respectively, in the placebo arm.

6.36 Change in the histology total activity score (ranges from 0 to 18, higher scores indicative of greater disease activity) was also assessed as a secondary endpoint based on renal biopsy findings. There was no apparent difference in terms of change in total activity score between arms at 6 months. Both arms showed marginal decreases in the total score, primarily due to reductions in endocapillary proliferation and leukocyte infiltration (markers of inflammation).

6.37 The trial also assessed disease-specific and health-related quality of life measures based on Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), SF-36v2, EQ-5D-5L and Patient Global Impression of Severity (PGI-S) questionnaires. The trial report noted that baseline scores for all quality of life measures reflected general population norm values and did not show any significant changes throughout the study. The results did not show any improvements in these measures in patients receiving iptacopan compared to placebo.

Study X2202

6.38 In patients with native kidneys, there was a statistically significant reduction in 24-hour UPCR after 12 weeks of treatment with iptacopan (adjusted geometric mean ratio to baseline 0.55 (80% CI 0.46, 0.65)). Results from the long-term extension study B12001B suggest that treatment effects were sustained for up to 3 years.

6.39 The native kidney cohort had a mean eGFR at baseline of 70.1 mL/min/1.73 m^2 (SD 35.1). There was a nominal increase in eGFR of 2.6 mL/min/1.73 m^2 at Week 12. Treatment with iptacopan was associated with improved or stable eGFR for up to 2 years, after which there was a decreasing trend over time with a noticeable decline at around 3 years compared to baseline (-11.1 mL/min/1.73 m^2). The study report stated that the decline was driven by 4 patients who experienced eGFR declines of more than 20 mL/min/1.73 m^2, one of whom commenced dialysis following a urinary tract infection. All other patients had marginal changes in eGFR.

6.40 In post-transplant patients with recurrent C3G, treatment with iptacopan was associated with a statistically significant reduction in C3 Deposit Score at 12 weeks from baseline. Results from the long-term extension study suggest that treatment effects were sustained for up to 1 year.

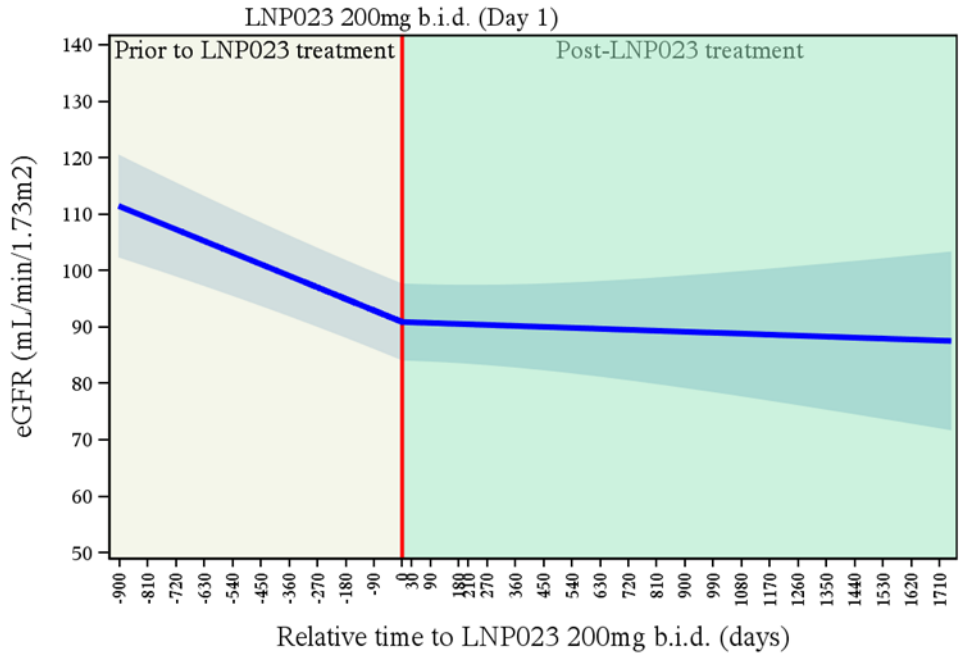
6.41 Most patients in the post-transplant cohort had baseline proteinuria values that were within the normal range (first morning void UPCR < 0.2 g/g), with a nominal reduction of 21% in UPCR observed at 12 weeks from baseline. The study report noted that the results should be interpreted with caution due to the small sample size and that further reductions in UPCR were unlikely given the cohort had relatively low levels of proteinuria at baseline. During the long-term extension study of up to 3 years, one patient had a UPCR just above the normal range while the remaining patients had values of 0.3 g/g or less.

6.42 Mean baseline eGFR in the post-transplant cohort was 52.6 mL/min/1.73 m^2 (SD 15.9). There was a slight decrease in eGFR at Week 12 which was not statistically significant (-0.61 mL/min/1.73 m^2, p = 0.78). Change in eGFR fluctuated throughout the study, ranging from -0.1 to -8.2 mL/min/1.73 m^2. The study report noted that 3 patients had reductions in eGFR of more than 20 mL/min/1.73 m^2 at any time, 2 of whom discontinued prematurely from the study. The remaining 7 patients had minimal changes in eGFR compared to baseline.

Pooled analysis

6.43 Figure 3 is a plot of annualised change in eGFR (pre- and post-treatment with iptacopan) based on the pooled analysis using available data from APPEAR-C3G, X2202 (native kidney cohort only) and B12001B including historical estimates collected prior to study entry (see also paragraph 6.15).

Figure 3: Pooled eGFR slope analysis based on the APPEAR-C3G trial, X2202 phase 2 study, B12001B extension study and historical data



Source: Figure 2.27, p135 of the submission
Abbreviations: b.i.d., twice a day; eGFR, estimated glomerular filtration rate; LNP023, iptacopan

6.44 The pre-treatment eGFR slope showed that patients were experiencing a rapid decline in kidney function (-8.32 mL/min/1.73 m^2 per year). In the post-treatment period, the slope was -0.70 mL/min/1.73 m^2 per year, resulting in a change in slope of 7.62 mL/min/1.73 m^2 per year that was of nominal statistical significance (95% CI 4.62, 10.62).

6.45 The submission claimed that the longer term eGFR slope analysis was more robust and clinically meaningful compared to shorter-term eGFR analyses in the key trial given the significant improvement in eGFR slope following initiation of treatment with iptacopan, thus supporting the potential for a delay in C3G disease progression. This claim appears optimistic given the attribution of a larger magnitude of benefit to iptacopan than observed during the randomised period of the trial (annualised eGFR slope difference between arms of 3.05 (95% CI -6.82, 12.92) mL/min/1.73 m^2/year).

6.46 The evaluation considered the results of the exploratory analysis should not be considered reliable due to heterogeneity across the included studies in terms of study design, duration and population characteristics, potential confounding due to differential use of supportive therapies and overall disease management between the pre- and post-treatment periods, and methodological limitations such as pooling of data from non-parallel observation periods. Overall, these limitations preclude any meaningful conclusions regarding long-term treatment effects with iptacopan compared to standard of care.

Comparative harms

6.47 All patients in the included studies received mandatory vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae type b*. Antibiotic prophylaxis could also be initiated if clinically appropriate.

6.48 Table 7 presents a summary of adverse events during the 6-month, double-blind period of the APPEAR-C3G trial.

Table 7: Summary of key adverse events in the APPEAR-C3G trial (6 months)

	Iptacopan N=38		Placebo N=36	
	Incidence, n (%)	Events, n (rate/100 pt-yrs) [a]	Incidence, n (%)	Events, n (rate/100 pt-yrs) [a]
Any AE	30 (78.9)	79 (431.8)	24 (66.7)	59 (331.3)
Severe AE	2 (5.3)	2 (10.9)	1 (2.8)	1 (5.6)
Serious AE	3 (7.9)	3 (16.4)	1 (2.8)	2 (11.2)
Fatal AE	0	0	0	0
AE leading to treatment discontinuation	0	0	0	0
AE leading to study drug interruption	4 (10.5)	6 (32.8)	4 (11.1)	4 (22.5)
AE requiring additional therapy	21 (55.3)	-	11 (30.6)	-
AE of special interest	4 (10.5)	-	2 (5.6)	-
Infections caused by encapsulated bacteria	2 (5.3)	3 (16.4)	1 (2.8)	1 (5.6)
- Otitis media	2 (5.3)	3 (16.4)	0	0
- Urethritis gonococcal	0	0	1 (2.8)	1 (5.6)
Serious or severe infections	2 (5.3)	2 (10.9)	0	0
- Blood culture positive	1 (2.6)	1 (5.5)	0	0
- Infected bite	1 (2.6)	1 (5.5)	0	0
Thyroid changes	0	0	1 (2.8)	1 (5.6)
- Blood thyroid stimulating hormone increased	0	0	1 (2.8)	1 (5.6)
Hypersensitivity	0	0	0	0
Testicular effects	0	0	0	0
Malignancy	0	0	0	0
Decreased platelets	0	0	0	0

Source: Table 2.42, p126; Table 2.46, p129 of the submission; Table 2-1, p37 of the CTD 2.7.4 summary of clinical safety v1.0 report; Table 14.3.1-1.10.3, p2008 of the APPEAR-C3G trial report

Abbreviations: AE, adverse event; pt-yrs, patient-years

[a] Exposure-adjusted event rates were only available for specific analyses (e.g. adverse events of special interest) in the trial report

6.49 Treatment with iptacopan was associated with a higher rate of adverse events compared to placebo. The most commonly occurring events (incidence > 10% in either treatment arm) were COVID-19 (21.1% versus 16.7% in the iptacopan and placebo arms, respectively), blood creatine phosphokinase increased (13.2% versus 2.8%) and nasopharyngitis (10.5% versus 2.8%).

6.50 Treatment with iptacopan was associated with an increased risk of serious adverse events compared to placebo. Serious adverse events of blood culture positive (for *Streptococcus pneumoniae*), chest discomfort and infected bite (organism not identified) were reported in 3 individual patients in the iptacopan arm, and acute kidney injury and ascites were reported in the same patient the placebo arm. There were no deaths reported during the double-blind period.

6.51 In terms of adverse events of special interest, treatment with iptacopan was associated with a higher incidence of infections (serious/severe or caused by encapsulated bacteria) compared to placebo.

6.52 The frequency of any adverse event for patients on iptacopan for up to 12 months (6 months double-blind and 6-months open-label extension) was similar to that reported during the double-blind period.

6.53 During the overall 12-month trial period, 6 participants (8.1%) who received iptacopan experienced serious adverse events: 4 patients who were on 12 months of iptacopan and 2 patients who switched from placebo to iptacopan in the open-label period. Additional serious adverse events reported in patients on 12 months of iptacopan were acute left ventricular failure, pneumococcal sepsis, pneumococcal pneumonia and streptococcal bacteraemia (evolved to septic shock) in the same patient; and retroperitoneal haematoma in one patient. Drug abuse (methamphetamine) and pneumonia (organism not identified) in one patient each were reported in patients who switched from placebo to iptacopan in the open-label period. There were no deaths throughout the trial period.

6.54 There are no comparative safety data for iptacopan in post-transplant patients with C3G recurrence. Data from non-randomised studies suggest treatment with iptacopan is associated with higher rates of serious adverse events in these patients compared to those with native kidneys.

6.55 The submission presented additional safety data from the X2202 phase 2 study, the B12001B extension study and the Periodic Safety Update Report (PSUR) for the 5 June 2024 to 4 December 2024 reporting period.

6.56 No new safety signals were identified during the reporting period. Infections caused by encapsulated bacteria (including *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae type b*) is an important identified risk. Important potential risks include serious haemolysis following discontinuation of iptacopan (specific to patients with PNH) and malignancies. Missing information includes use in pregnancy and long-term safety (exposure > 2 years).

6.57 The PSUR stated that the safety and efficacy of iptacopan in patients aged less than 18 years have not been established. A paediatric clinical development program is in place and there is one ongoing clinical trial enrolling paediatric patients with C3G (APPEAR-C3G).

Benefits/harms

6.58 On the basis of direct evidence presented in the submission, in patients with C3G who have native kidneys, for every 100 patients treated with iptacopan in comparison with placebo:

- Approximately 24 additional patients would have at least 50% reduction in proteinuria (a marker of kidney injury) at 6 months.
- There would be no apparent difference in renal function based on eGFR at 6 months.

- There would be no apparent difference in quality of life measures at 6 months.
- There would be approximately 5 additional patients with serious or severe infections at 6 months.

6.59 A benefits/harms comparison was not presented for post-transplant patients with C3G recurrence due to a lack of comparative efficacy and safety data.

Clinical claim

6.60 The submission described iptacopan as superior in terms of efficacy compared to standard of care in patients with C3G who have native kidneys. The evaluation considered this claim may be reasonable in terms of short-term reductions in proteinuria but was inadequately supported in terms of changes in eGFR and longer-term reductions in the risk of progression to end-stage kidney disease. The ESC considered that it was plausible that the improvement in proteinuria should result in improved kidney function and reduced risk of end-stage kidney disease, but the magnitude of the effect is unknown.

6.61 The submission described iptacopan as inferior in terms of safety compared to standard of care in patients with C3G who have native kidneys. The ESC agreed with the evaluation that this claim was reasonable.

6.62 The submission described iptacopan as superior in terms of efficacy but inferior in terms of safety compared to standard of care in patients with C3G disease recurrence following kidney transplantation. The ESC agreed with the evaluation that this claim was inadequately supported as there are no comparative data in this group of patients.

6.63 The following issues should be considered regarding the submission claims:

- The clinical claim of superiority is based on short-term biomarkers of proteinuria reduction but no apparent difference in terms of change in eGFR compared with placebo in the key trial. The pooled eGFR slope analysis should not be considered robust given heterogeneity between the included studies in terms of study design, duration and populations, methodological limitations (pooling of data from non-parallel observation periods) as well as potential confounding with substantial differences in terms of use of supportive therapies during the pre- and post-randomisation periods of the analysis.
- There are no data supporting long-term outcomes with iptacopan treatment such as delay or avoidance of end-stage kidney disease (and treatment modalities such as dialysis and transplant) and associated survival benefits. There is a biological rationale and epidemiological evidence supporting proteinuria and eGFR levels as prognostic variables for kidney disease progression. However, the magnitude by which proteinuria reduction or eGFR stabilisation mitigates progression to ESKD and its associated sequelae remains uncertain.
- The applicability of the APPEAR-C3G trial to the Australian setting is uncertain given the lack of Australian data on patients with C3G. There were differences in

terms of demographics and markers of disease severity when comparing the trial population with data from UK (RaDaR) and Spanish (GLOSEN) disease registries. There were limited subgroup data available, and it was unclear whether there are any potential treatment effect modifiers in terms of baseline characteristics. The ESC noted that there was a high level of variation in characteristics across the three cohorts (APPEAR-C3G, RaDaR and GLOSEN) and considered the APPEAR-C3G population is likely to be reasonably representative of the Australian PBS population.

- The risk-benefit profile of iptacopan in post-transplant patients with disease recurrence is uncertain, with no comparative efficacy or safety data in this group of patients.

6.64 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data as it was based on short-term biomarkers (proteinuria reduction), with no demonstrated difference in terms of change in eGFR compared to placebo.

6.65 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.66 The submission presented a stepped economic evaluation of iptacopan compared to placebo for the treatment of C3G in adult patients with native kidneys. The economic evaluation was based on the APPEAR-C3G trial, X2202 phase 2 study and the B12001B extension study, with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.67 The submission also presented a scenario analysis assessing the cost effectiveness of iptacopan compared to placebo in post-transplant patients who experience disease recurrence.

6.68 Key components of the economic evaluation are summarised in Table 8.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost effectiveness/cost utility analysis
Outcomes	Proportion of patients with proteinuria reduction, change in eGFR over time, life years, quality adjusted life years
Time horizon	70 years (lifetime)
Methods used to generate results	Markov cohort analysis
Perspective	Societal (inclusion of productivity losses)
Treatments	Iptacopan or placebo (in combination with standard of care therapies)
Model structure	9 health states including CKD Stage 1, 2, 3a, 3b, 4, 5, dialysis, post-transplant (successful graft) and post-transplant (graft failure) as well as death.
Cycle length	13 weeks (half cycle correction)
Patient characteristics	Baseline age, sex and initial distribution of patients across CKD stages were based on reported baseline values from the combined treatment arms of the APPEAR-C3G trial.

<table>
<tr><th>Component</th><th>Description</th></tr>
<tr><td>Transition probabilities</td><td>The risk of treatment discontinuation in the iptacopan arm was based on the APPEAR-C3G trial and B12001B extension study for the first 1.5 years of the model (5.3% annual probability based on 3/38 patients who discontinued during APPEAR-C3G and B12001B) while discontinuation rates over the longer term were assumed (1%).

The risk of CKD progression and dialysis were based on the mean change in eGFR per year in each treatment arm, which were converted to transition probabilities by estimating the total time it would take to transition from the midpoint of each CKD stage to the midpoint of the next CKD stage. It was assumed that all patients with an eGFR < 7 mL/min/1.73 m^2 would initiate dialysis.

Treatment with iptacopan was assumed to prevent all C3G-mediated changes in kidney function, with treated patients adopting the same eGFR decline over time as prospective living kidney donors registered at UK renal treatment centres between 2003-2015 (Fenton 2018). The change in eGFR in the placebo arm was based on the mean change in eGFR per year reported in the pre-iptacopan period in the pooled analysis of APPEAR-C3G, X2202, B12001B studies. The change in eGFR in the placebo arm was extrapolated over time assuming a constant linear decline in kidney function.

The probability of transplantation in CKD Stage 5 patients, the probability of transplantation in dialysis patients and the probability of transplant graft rejection were based Australia and New Zealand Dialysis and Transplant Registry (47th Annual Report 2024).

The risk of death was estimated based on Australian life tables (ABS 2021-2023) with additional risk multipliers for different health states based on standardised mortality rates for patients with and without kidney failure reported in a retrospective cohort study of rare kidney diseases in the United Kingdom (Wong 2024; RaDaR registry).</td></tr>
<tr><td>Utility values</td><td>Health state utility values were estimated based on EQ-5D-5L index scores (UK value set) reported in a vignette study describing health states for primary hyperoxaluria type 1 in the UK general population (de Freitas 2023).

The health state utility for post-transplantation (successful graft) was assumed to be the same as CKD Stage 1/2. The health state utility for post-transplantation (graft failure) was assumed to be the same as dialysis.

The submission also provided alternative utility values based on estimates reported in an Australian cost of illness study for chronic kidney disease (Deloitte 2023).

Health state utility values used in the economic evaluation and in Deloitte 2023
<table>
<tr><th rowspan="2">Health states</th><th colspan="2">De Freitas (2023)</th><th rowspan="2">Deloitte 2023</th></tr>
<tr><th>EQ-5D-5L</th><th>TTO</th></tr>
<tr><td>CKD 1-2</td><td>0.68</td><td>0.88</td><td>0.85</td></tr>
<tr><td>CKD 3a</td><td>0.63</td><td>0.86</td><td>0.80</td></tr>
<tr><td>CKD 3b</td><td>0.57</td><td>0.80</td><td>0.80</td></tr>
<tr><td>CKD 4</td><td>0.33</td><td>0.51</td><td>0.74</td></tr>
<tr><td>CKD 5 (conservative care)</td><td>0.02[a]</td><td>0.39[a]</td><td>0.73</td></tr>
<tr><td>Dialysis</td><td>0.02[a]</td><td>0.39[a]</td><td>0.67</td></tr>
<tr><td>Post-transplant (functioning kidney)</td><td>0.68</td><td>0.77</td><td>0.83</td></tr>
<tr><td>Post-transplant (graft failure)</td><td>0.02[b]</td><td>0.39[b]</td><td>0.67[b]</td></tr>
</table></td></tr>
</table>

Component	Description
Costs	Drug costs were estimated based on the proposed effective price of iptacopan. Drug costs for standard therapy (ACEI/ARB, corticosteroids, immunosuppressants and SGLT2 inhibitors) were based on published PBS prices. The cost of pneumococcal vaccination was estimated based on prices reported on the Eastern Health Authority website (a service provider in Adelaide). Transplantation event costs were estimated based on values presented in an Australian cost of illness study for chronic kidney disease (Deloitte 2023) with the weighting between live and deceased donors recalculated based on data from the Australia and New Zealand Dialysis and Transplant Registry (47th Annual Report 2024). Health state costs for CKD stages and dialysis were estimated based on values presented in an Australian cost of illness study for chronic kidney disease (Deloitte 2023). The average cost of dialysis was recalculated based on the use of peritoneal dialysis, home haemodialysis, satellite dialysis and hospital dialysis from the Australia and New Zealand Dialysis and Transplant Registry (47th Annual Report 2024). The health state cost for post-transplantation (successful graft) was estimated based on values reported in the dapagliflozin (chronic kidney disease) Public Summary Document (PSD) July 2021 PBAC meeting. The health state cost of post-transplantation (graft failure) was assumed to be the same as dialysis. Errors in the implementation of transplant event costs and kidney failure health state costs were corrected in the commentary.
Discount rate	3.5% for costs and outcomes
Software package	Microsoft Excel

Source: Section 3.3-3.6, pp154-196 of the submission
Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PBS, Pharmaceutical Benefits Scheme; PSD, Public Summary Document; RaDaR, United Kingdom National Registry of Rare Kidney Disease; SGLT2, sodium-glucose co-transporter 2

6.69 Patients entered the model with chronic kidney disease but without kidney failure (Stage 1, 2, 3a, 3b or 4) based on the distribution of patients in the APPEAR-C3G trial. In each 13-week cycle, patients could remain in their current health state, progress to more severe kidney disease or die. Patients who reached CKD Stage 5 could remain on conservative care (until eGFR < 7 mL/min/1.73 m^2), switch to dialysis or undergo transplantation. Patients using dialysis could remain in this state or undergo transplantation. After transplantation, patients transitioned to the post-transplant (successful graft) health state and could remain in this state or transition to the post-transplant (graft failure) health state. Patients in the post-transplant (graft failure) health state could remain in this state or undergo another transplant.

6.70 The ESC noted that the model structure was similar to other published models in chronic kidney disease, however the model was built around a difference in eGFR decline between treatment arms which was not supported by the key randomised trial for iptacopan (APPEAR-C3G) which demonstrated a statistically significant improvement in proteinuria but not eGFR between treatment arms.

6.71 Additionally, expert advice from the sponsor's advisory panel indicated that disease trajectories for C3G were more unpredictable than other kidney conditions due to the relapsing-remitting pattern of disease, noting that patients may have periods of stability followed by episodes of rapid progression (C3G Advisory Board 9 May 2025; Attachment 6 of the submission). This pattern was not reflected in the model structure

used in the submission. The PSCR stated that the model was structured to reflect the average progression of C3G across the patients over time at a population level.

6.72 The submission nominated a 3.5% discount rate for costs and outcomes on the basis that the Health Technology Assessment Policy and Methods Review (2024) recommended a reduction in the discount rate to no lower than 3.5% for interventions whose benefits accrue over a long period (Recommendation 39). However, the current PBAC Guidelines state that the base case economic analysis should use a 5% discount rate for costs and outcomes with other discount rates tested in sensitivity analysis. Therefore, during the evaluation the base case analysis was respecified using a 5% discount rate.

6.73 The submission nominated a societal perspective for the economic analysis due to the unique socioeconomic burden associated with C3G, which disproportionately affects younger individuals who are often in critical phases of their education, early career development, or prime working years. The submission stated that omitting the productivity costs would underestimate the real-world impact of C3G, misrepresenting the value of interventions meant to address the disease. However, the current PBAC Guidelines state that the base case economic analysis should use a healthcare system perspective, which can be supported with additional supplementary analyses using a broader societal perspective. Therefore, during the evaluation the base case analysis was respecified using a healthcare system perspective.

6.74 Key drivers of the economic model are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Change in eGFR over time	The change in eGFR over time in the iptacopan arm was based on the assumption that treatment would prevent all C3G-mediated changes in kidney function with treated patients adopting the same eGFR decline as prospective living kidney donors registered at UK renal treatment centres between 2003-2015 (Fenton 2018). The submission claimed this assumption was reasonable as the mean change in eGFR per year reported in the post-iptacopan period from the pooled analysis of APPEAR-C3G, X2202, B12001B studies was similar to general population estimates. The PSCR also maintained this assumption was reasonable based on stabilisation of renal decline in patients treated with iptacopan. Expert advice from the sponsor's advisory panel noted that this assumption may be optimistic, but it was reasonable to expect that iptacopan treatment may substantially slow the rate of eGFR decline relative to placebo (C3G Advisory Board 9 May 2025; Attachment 6 of the submission). The ESC noted that this assumption represents the most optimistic scenario of treatment effect and is not considered plausible. The submission estimated the change in eGFR over time in the placebo arm based on the mean change in eGFR per year using data reported in the pre-iptacopan period from the pooled analysis of APPEAR-C3G, X2202, B12001B studies.	High, favours iptacopan

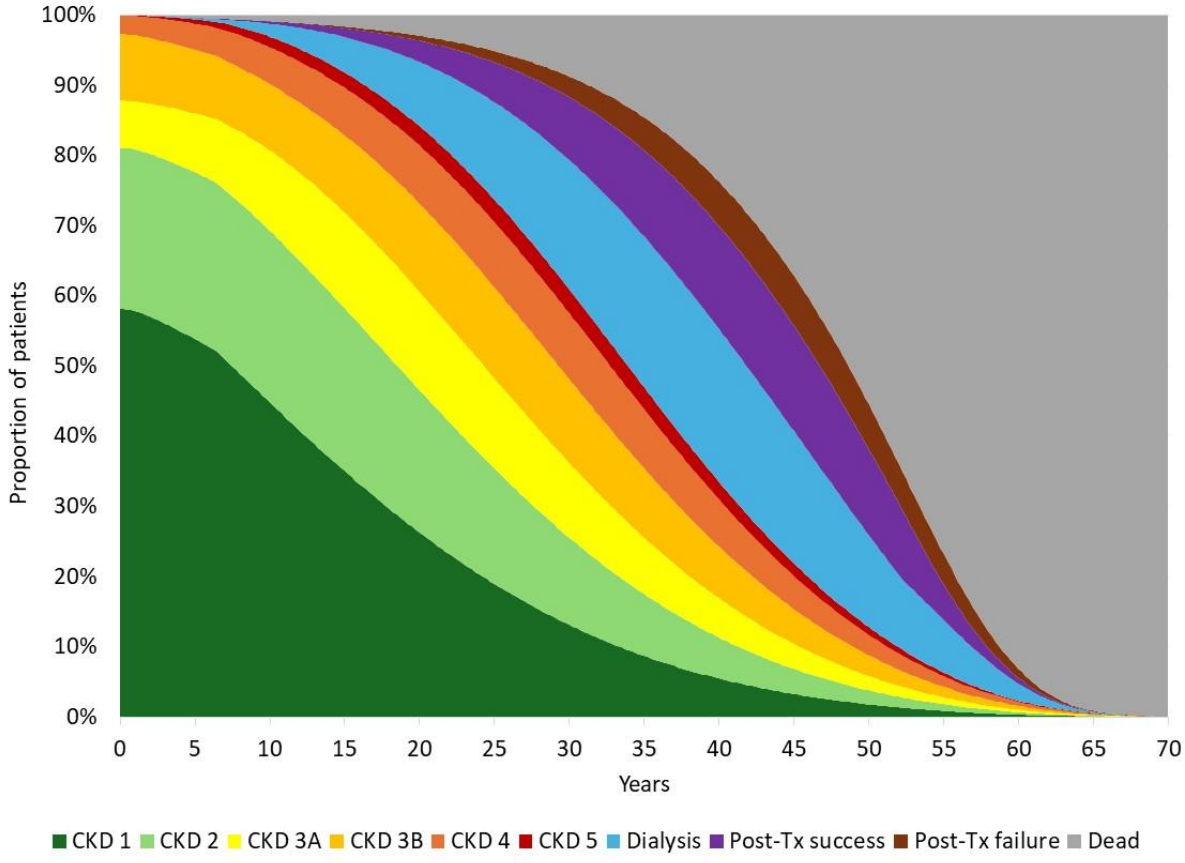
Description	Method/Value	Impact
	The ESC agreed with the evaluation that the validity of the pooled analysis was uncertain due to heterogeneity between the included studies in terms of study design, duration and populations, methodological limitations (pooling of data from non-parallel observational periods), as well as potential confounding due to substantial differences in the use of supportive therapies during the pre-randomisation and post-randomisation periods of the APPEAR-C3G trial. The ESC considered that estimates of eGFR decline for the placebo arm from the APPEAR-C3G trial alone would be more appropriate and observed differences during the double-blind period would provide a more robust representation of treatment effects associated with iptacopan rather than observational comparisons of 'before and after' iptacopan treatment. The estimated decrease in eGFR over time from the pooled analysis was substantially larger than natural history cohorts from the RaDaR (predominantly younger C3G patients likely to have more progressive disease than the broader population) and GLOSEN registries (subset of C3G patients who progressed to kidney failure). The PSCR argued that this was because those populations have a different baseline risk of disease progression. The change in eGFR in the placebo arm was extrapolated over time assuming a constant linear decline in kidney function. Expert advice from the sponsor's advisory panel acknowledged that this was a convention frequently used in CKD models but noted that this may not be reflective of C3G which has a relapsing-remitting pattern of disease, with periods of stability followed by episodes of rapid progression (C3G Advisory Board 9 May 2025; Attachment 6 of the submission). Overall, the inclusion of a modelled difference in eGFR over time between iptacopan and placebo was not supported by data from the APPEAR-C3G trial which failed to demonstrate a statistically significant difference between treatment arms at 6 months (treatment difference: 2.16; 95% CI -2.75, 7.06).	
Health state utility values	Health state utility values for CKD stages and kidney failure health states were estimated based on EQ-5D-5L index scores (UK value set) reported in a vignette study describing health states for primary hyperoxaluria type 1 (PH1) in the UK general population (de Freitas 2023). The submission claimed that this data source is directly relevant to C3G, as PH1 is another rare disease with a similar age of onset, severe disease trajectory (rapidly progressive kidney disease leading to dialysis and transplantation) and symptom burden. The ESC agreed with the evaluation that use of these values was not appropriate as the vignettes describing PH1 health states did not appear to be comparable to C3G health states. In particular, the vignette for CKD Stage 5 describes a health state in which patients require hospital haemodialysis 5 days a week for several hours per day; experience kidney stones, nausea, bone pain and black sores on their skin which are difficult to treat; feel tired, anxious and/or depressed; are unable to carry out activities of daily living; and are awaiting a combined liver and kidney transplant. This description may not be representative of a CKD Stage 5 disease state in patients with C3G. The valuation of the PH1 health states by the general public using the EQ-5D-5L instrument resulted in extremely low utility values (CKD Stage 5: 0.02). Estimates from the de Frietas (2023) publication using a TTO approach generally resulted in higher utility values (CKD Stage 5: 0.39) but remained lower than typically observed in CKD populations (CKD Stage 5: 0.54-0.73; dialysis: 0.44-0.79; Cooper 2020 systematic review).	High, favours iptacopan

Description	Method/Value	Impact
	Additionally, the sponsor did provide any results from a *post hoc* analysis of utility scores from the APPEAR-C3G trial, which may have been informative in determining the most relevant utility estimates. The ESC noted that trial-based utilities are preferred by the PBAC as outlined in the PBAC Guidelines (v5.0) and considered that the values from the APPEAR-C3G trial may be informative. In the absence of trial-based utilities, the ESC considered that the values reported in Deloitte 2023 appear to be the most reasonable. The pre-PBAC response argued that these utility values are reflective of an elderly, general CKD population.	

Source: Constructed during the evaluation.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TTO, time trade off

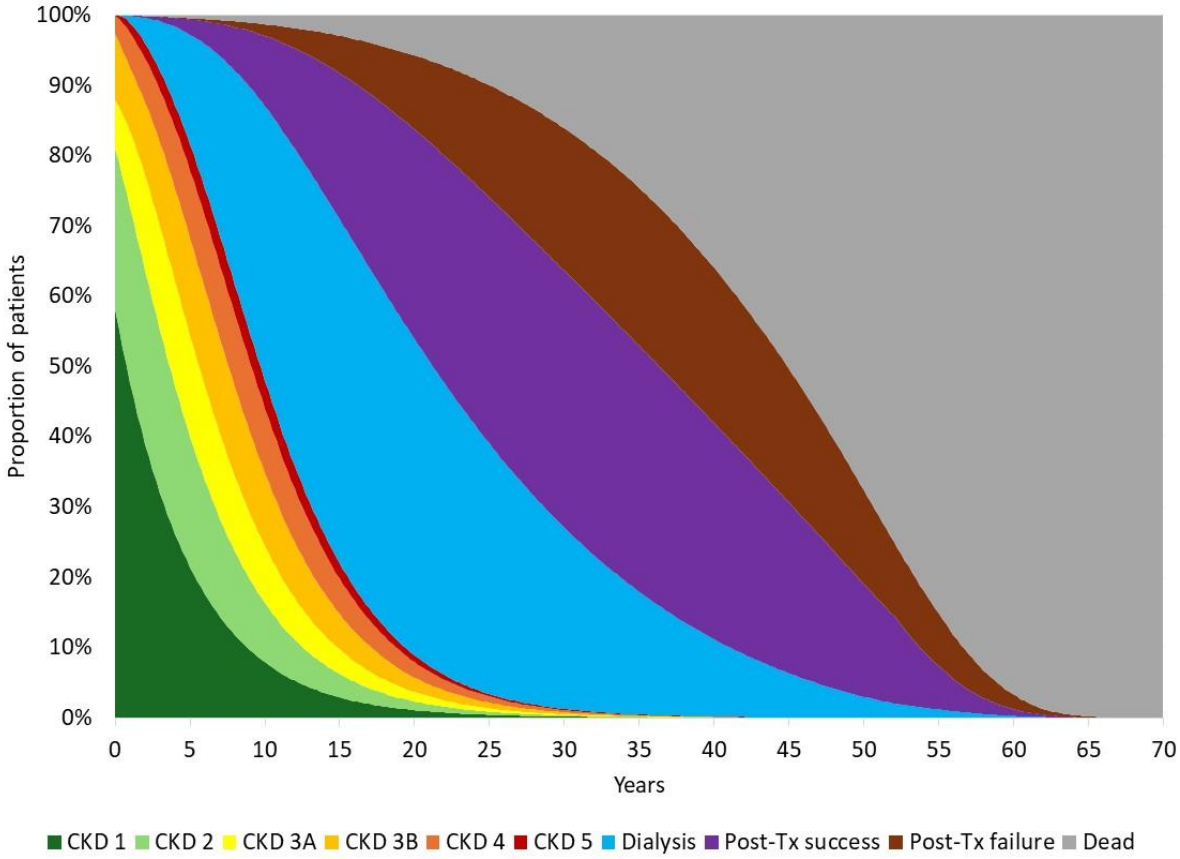
6.75 The estimated differences in eGFR change over time between treatment arms resulted in substantial differences in the time spent in modelled CKD states over time. Patients in the iptacopan treatment arm showed a gradual progression through CKD stages over time with progression largely driven by the estimated discontinuation rate for iptacopan, as patients who remained on therapy were expected to have only small changes in eGFR over time, consistent with the general population. Meanwhile, patients in the placebo arm spent a prolonged period of time in the dialysis and post-transplantation (graft failure) health states (approximately 20 years in total) with extremely low utility values (0.02 utility). The ESC considered that it was unclear whether the modelled duration of survival in the dialysis and post-transplant (graft failure) states was clinically plausible. See figures below.

Figure 4: Proportion of patients in different health states over time in the modelled iptacopan treatment arm



Source: 'Iptacopan economic model' provided with the submission
Abbreviations: CKD, chronic kidney disease; Post-Tx, post-transplant

Figure 5: Proportion of patients in different health states over time in the modelled placebo treatment arm



Source: 'Iptacopan economic model' provided with the submission
Abbreviations: CKD, chronic kidney disease; Post-Tx, post-transplant

6.76 Disaggregated health outcomes estimated in the model are summarised in Table 10.

Table 10: Summary of health outcomes estimates in the economic evaluation

Health outcome	Iptacopan	Placebo	Incremental outcome
Time on iptacopan treatment, years	26.54	0.00	26.54
Events per 100 patients			
Transplantations	50	121	-71
Adverse events	0	0	0
Life years			
CKD Stage 1/2	19.7701	5.1620	14.6081
CKD Stage 3/4	13.1412	5.0119	8.1293
CKD Stage 5 (conservative care)	1.1585	0.6077	0.5508
Dialysis	6.6792	12.4699	-5.7906
Post-transplant (successful graft)	3.9773	12.3857	-8.4084
Post-transplant (graft failure)	1.7911	7.0316	-5.2405
Total life years (undiscounted)	46.5173	42.6686	3.8487
Total life years (discounted)	**17.9534**	**17.3548**	**0.5986**
Quality adjusted life years			
CKD Stage 1/2	13.4437	3.5101	9.9335
CKD Stage 3/4	6.9461	2.5996	4.3465
CKD Stage 5 (conservative care)	0.0232	0.0122	0.0110
Dialysis	0.1336	0.2494	-0.1158
Post-transplant (successful graft)	2.7046	8.4223	-5.7177
Post-transplant (graft failure)	0.0358	0.1406	-0.1048
Total quality adjusted life years (undiscounted)	23.2829	14.9342	8.3527
Total quality adjusted life years (discounted)	**10.2660**	**6.8135**	**3.4526**

Source: Table 3.39, pp203-204 of the submission; 'Iptacopan economic model' provided with the submission.
Abbreviations: LY, life year; QALY, quality adjusted life year

6.77 The results of the modelled economic evaluation are summarised in Table 11.

Table 11: Results of the modelled economic evaluation (*selected steps*)

Step and component	Iptacopan	Placebo	Increment
Step 1: Proportion of patients with ≥50% reduction in proteinuria from the APPEAR-C3G trial. Iptacopan drug costs for 6 months			
Costs	$[redacted][3]	$[redacted][1]	$[redacted][3]
Responders	29.7%	5.6%	24.2%
Incremental cost per responder			**$[redacted][5]**
Step 4: Annualised change in eGFR for the placebo arm based on the pre-iptacopan period from the pooled analysis of APPEAR-C3G, X2202, B12001B. Annualised change in eGFR for the iptacopan arm assumed to be the same as the general population. Include health state utility values and iptacopan drug costs for 6 months			
Costs	$[redacted][3]	$[redacted][1]	$[redacted][3]
QALYs	0.3243	0.3214	0.0029
Incremental cost per QALY gained			**$[redacted][7]**
Step 6a: Extrapolated to 1 year (discounting applied)			
Costs	$[redacted][4]	$[redacted][1]	$[redacted][4]
QALYs	0.6406	0.6288	0.0118
Incremental cost per QALY gained			**$[redacted][7]**
Step 6b: Extrapolated to 5 years (discounting applied)			
Costs	$[redacted][7]	$[redacted][2]	$[redacted][7]
QALYs	2.8935	2.5911	0.3024
Incremental cost per QALY gained			**$[redacted][7]**
Step 6d: Extrapolated to 70 years (discounting applied)			
Costs	$[redacted][7]	$[redacted][5]	$[redacted][7]
Life years	17.9534	17.3548	0.5986
QALYs	10.2660	6.8135	3.4526
Incremental cost per life year gained			**$[redacted][7]**
Incremental cost per QALY gained			**$[redacted][6]**

Source: Table 3.36, p202; Table 3.37, 202; Table 3.40, p204 of the submission; 'Iptacopan economic model' provided with the submission.
Abbreviations: QALY, quality adjusted life year
Note: During the evaluation the base case was respecified using a 5% discount rate, removing societal costs and correcting for errors in transplantation event costs and post-transplantation (graft failure) health state costs
The redacted values correspond to the following ranges:
[1]*$0 to < $5,000*
[2]*$35,000 to < $45,000*
[3]*$135,000 to < $155,000*
[4]*$255,000 to < $355,000*
[5]*$555,000 to < $655,000*
[6]*$955,000 to < $1,055,000*
[7]*> $1,055,000*

6.78 Based on the economic model, treatment with iptacopan was associated with an incremental cost per QALY gained of$955,000 to < $1,055,000 compared to placebo for the treatment of C3G in adult patients with native kidneys.

6.79 The submission acknowledged that the incremental cost effectiveness ratio for iptacopan exceeded typical funding thresholds but noted that the PBAC has considered estimates as high as $855,000 to $955,000 per QALY gained in special circumstances (nusinersen Public Summary Document [PSD], March 2022 PBAC meeting). The submission argued that given the clinical severity of C3G, the high unmet need, and the rarity of the disease, a cost effectiveness estimate in this range may be considered reasonable within the context of PBAC decision-making for high-need, low-prevalence diseases. The ESC noted that in other kidney-specific conditions the PBAC has recommended treatments with substantially lower ICERs, though

recognised that the prevalence of the condition, the degree of confidence in the modelled outcomes, and financial impact are also relevant considerations. A summary of PBAC considerations of treatments for kidney-specific indications is shown in Table 12. The pre-PBAC response noted that for lumasiran in PH1, the PBAC considered an average cost per patient per year due to the high unmet clinical need, the rare nature of the disease, and uncertainty in the economic model and ICER. The sponsor considered that as C3G shares similarities with PH1 in terms of the challenges of economic modelling in an ultra-rare disease, a similar approach would be welcomed by the sponsor.

Table 12: PBAC considerations of other treatments for kidney-specific indications.

Treatment	Condition	PBAC Meeting	ICER Range	Financial Impact (first 6 years)
Finerenone (Kerendia®)	CKD with Type 2 diabetes	Jul-22 Mar-23	$5,000 to < $15,000 per QALY	$80 million to < $90 million
Dapagliflozin (Forxiga®)	CKD	Jul-21 Sep-21 Nov-21 Mar-22	Dapagliflozin dominant over SoC (uncertain)	$200 million to < $600 million per year
Empagliflozin (Jardiance®)	CKD	Nov-23 May-25	Cost-minimisation vs dapagliflozin 5,000 to < $15,000 per QALY	NA $200 million to < $300 million in the first six years of listing
Lumisiran (Oxlumo®)	PH1	Mar-25	$455,000 to < $555,000 per QALY gained - PBAC recommended a cost per patient	$10 - $20M per year
Tolvaptan (Jinarc®)	ADPKD	Mar-18 Jul-18	$15,000/QALY - $45,000/QALY (TEMPO 3:4 population) Dominant (REPRISE population)	$30 - $60 million over the first 6 years

Source: finerenone-psd-july-2022, finerenone-psd-03-2023, dapagliflozin-ckd-psd-nov-2021, dapagliflozin-psd-march-2022, empagliflozin-psd-nov-2023, lumasiran-psd-march-2025, tolvaptan-psd-july-2018

ADPKD, autosomal-dominant polycystic kidney disease; CKD, chronic kidney disease; PH1, primary hyperoxaluria type 1; QALY, quality-adjusted life years

6.80 The evaluation and the ESC considered the cost-effectiveness estimate should not be considered reliable as the model was built around a difference in eGFR decline between treatment arms which was not supported by the APPEAR-C3G trial, the structure of the model did not reflect the underlying relapsing-remitting pattern of disease, and the utility values used in the model appeared extremely low for health states in which modelled patients spend prolonged periods of time (particularly dialysis and graft failure).

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

Table 13: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALYs	ICER	Change from base case ICER
Revised base case	$[redacted]	**3.4526**	$[redacted]	**-**
Discount rate (revised base case: 5% for benefits and costs)				
3.5% discount rate	$[redacted]	4.3562	$[redacted]	[redacted]%
0% discount rate	$[redacted]	8.3527	$[redacted]	[redacted]%
Time horizon (revised base case: 70 years)				
50 years	$[redacted]	3.4321	$[redacted]	[redacted]%
30 years	$[redacted]	3.1889	$[redacted]	[redacted]%
10 years	$[redacted]	1.0894	$[redacted]	[redacted]%
Change in eGFR over time (revised base case: change in placebo arm -8.32 mL/min/1.73 m^2 per year, based on pooled eGFR slope analysis; patients who remained on iptacopan therapy assumed to follow general population changes in eGFR over time; all patients assumed to have native kidneys)				
Annual change in placebo arm based on the APPEAR-C3G trial (-3.079 mL/min/1.73 m^2 per year)	$[redacted]	2.1537	$[redacted]	[redacted]%
Annual change in placebo arm based on RaDaR registry (-4.90 mL/min/1.73 m^2 per year)	$[redacted]	2.9053	$[redacted]	[redacted]%
Annual change in placebo arm based on the subset of patients that progressed to kidney failure in GLOSEN registry (-6.50 mL/min/1.73 m^2 per year)	$[redacted]	3.2484	$[redacted]	[redacted]%
Change in iptacopan arm based on 25% of the change in placebo arm	$[redacted]	2.1151	$[redacted]	[redacted]%
Change in iptacopan arm based on 50% of the change in placebo arm	$[redacted]	1.1589	$[redacted]	[redacted]%
Change in iptacopan arm based on 75% of the change in placebo arm	$[redacted]	0.4854	$[redacted]	[redacted]%
Change in iptacopan arm based on 100% of the change in placebo arm	$[redacted]	0.0000	Dominated	NA
Maximum duration of iptacopan benefit limited to 10 years	$[redacted]	1.9681	$[redacted]	[redacted]%
Maximum duration of iptacopan benefit limited to 20 years	$[redacted]	2.8716	$[redacted]	[redacted]%
Maximum duration of iptacopan benefit limited to 30 years	$[redacted]	3.2694	$[redacted]	[redacted]%
Maximum duration of iptacopan benefit limited to 40 years	$[redacted]	3.4093	$[redacted]	[redacted]%
Kidney replacement therapies (revised base case: assume all patients with an eGFR < 7 mL/min/1.73 m^2 would use dialysis, with transplantation probabilities estimated from the ANZDATA 2024, 47th Annual Report)				
Transplantation rate from dialysis based on younger patients aged 15 to 64 years (ANZDATA)	$[redacted]	2.8950	$[redacted]	[redacted]%
Graft failure rate based on graft failures only (ANZDATA) instead of combined estimate of graft failure and death with functioning graft	$[redacted]	3.0852	$[redacted]	[redacted]%
Utility values (revised base case: based on EQ-5D-5L health state utility values reported in de Freitas 2023 for primary hyperoxaluria type 1)				
Health state utility values based on TTO estimates from de Freitas 2023	$[redacted]	3.0591	$[redacted]	[redacted]%
Health state utility values based on EQ-5D-3L estimates from Deloitte 2023	$[redacted]	1.3460	$[redacted]	[redacted]%
Costs (revised base case: various published sources)				
Include productivity costs from Deloitte 2023 [a]	$[redacted]	3.4526	$[redacted]	[redacted]%

Source: Table 3.43, pp208-210 of the submission; 'Iptacopan economic model' provided with the submission

Abbreviations: ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; CI, confidence interval; CKD, chronic kidney disease; GLOSEN, Spanish Group for the Study of Glomerular Disease; ICER, incremental cost effectiveness ratio; NA, not applicable; QALYs, quality adjusted life years; RaDaR, United Kingdom National Registry of Rare Kidney Diseases; TTO, time trade off

[a] Includes costs for reduced employment, premature mortality, absenteeism, presenteeism and informal care in patients with mid-stage kidney disease or kidney failure (Deloitte 2023 report)

Note: During the evaluation the base case was respecified using a 5% discount rate, removing societal costs and correcting for errors in transplantation event costs and post-transplantation (graft failure) health state costs
The redacted values correspond to the following ranges:
[1]*$755,000 to < $855,000*
[2]*$855,000 to < $955,000*
[3]*$955,000 to < $1,055,000*
[4]*> $1,055,000*

6.82 The results of the sensitivity analyses indicate that the model is most sensitive to time horizon (but only at 10 years, not 30 years), annual change in eGFR over time in the placebo arm, the modelled treatment effect for iptacopan and health state utility values.

6.83 Multivariate sensitivity analyses were conducted during the evaluation due to the high degree of uncertainty associated with the modelled estimates. These analyses were conducted by varying the change in eGFR over time in the placebo arm, the modelled treatment effect for iptacopan and health state utility values (summarised in Table 14).

Table 14: Multivariate sensitivity analyses

Cost per QALY gained (change from base case ICER)	Iptacopan eGFR change based on general population	Iptacopan eGFR change based on 25% of placebo	Iptacopan eGFR change based on 50% of placebo	Iptacopan eGFR change based on 75% of placebo
Using EQ-5D-5L health state utility values reported in de Freitas 2023				
Annual eGFR change in placebo arm based on the pooled analysis of iptacopan studies (-8.32 mL/min/1.73 m^2 per year)	$[redacted][1] **[base case]**	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted])	$[redacted][2] ([redacted])
Annual eGFR change in placebo arm based on the subset of patients that progressed to kidney failure in GLOSEN registry (-6.50 mL/min/1.73 m^2 per year)	$[redacted][2] ([redacted])	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Annual eGFR change in placebo arm based on RaDaR registry (-4.90 mL/min/1.73 m^2 per year)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Annual eGFR change in placebo arm based on the APPEAR-C3G trial (-3.079 mL/min/1.73 m^2 per year) [2]	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Using TTO health state utility values reported in de Freitas 2023				
Annual eGFR change in placebo arm based on the pooled analysis of iptacopan studies (-8.32 mL/min/1.73 m^2 per year)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Annual eGFR change in placebo arm based on the subset of patients that progressed to kidney failure in GLOSEN registry (-6.50 mL/min/1.73 m^2 per year)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Annual eGFR change in placebo arm based on RaDaR registry (-4.90 mL/min/1.73 m^2 per year)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Annual eGFR change in placebo arm based on the APPEAR-C3G trial (-3.079 mL/min/1.73 m^2 per year)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Using EQ-5D-3L health state utility values reported in Deloitte 2023				
Annual eGFR change in placebo arm based on the pooled analysis of iptacopan studies (-8.32 mL/min/1.73 m^2 per year)	$[redacted][2] [redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Annual eGFR change in placebo arm based on the subset of patients that progressed to kidney failure in GLOSEN registry (-6.50 mL/min/1.73 m^2 per year)	$[redacted][2] [redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Annual eGFR change in placebo arm based on RaDaR registry (-4.90 mL/min/1.73 m^2 per year)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)
Annual eGFR change in placebo arm based on the APPEAR-C3G trial (-3.079 mL/min/1.73 m^2 per year)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][2] ([redacted]%)

Source: 'Iptacopan economic model' provided with the submission.

Abbreviations: eGFR, estimated glomerular filtration rate; GLOSEN, Spanish Group for the Study of Glomerular Disease; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; RaDaR, United Kingdom National Registry of Rare Kidney Diseases; TTO, time trade off

Note: During the evaluation the base case was respecified using a 5% discount rate, removing societal costs and correcting for errors in transplantation event costs and post-transplantation (graft failure) health state costs

The redacted values correspond to the following ranges:

[1] *$955,000 to < $1,055,000*

[2] *> $1,055,000*

6.84 The multivariate analyses demonstrated that the estimated cost per QALY gained with iptacopan compared to placebo could be substantially higher than estimated in the revised base case.

6.85 The ESC noted that multivariate analyses produced large variations in the ICER, with values up to > $1,055,000/QALY based on a range of plausible estimates. The ESC considered the base case ICER presented was likely underestimated due to the issues outlined above regarding the change in eGFR over time in the placebo arm, the modelled treatment effect for iptacopan and health state utility values. A respecified (and still favourable) base case was suggested using annual change in placebo arm based on the APPEAR-C3G trial (-3.079 mL/min/1.73 m2 per year), Deloitte health utilities, and change in eGFR over time for iptacopan 50% of placebo. The ESC noted this resulted in an ICER of > $1,055,000/QALY ([redacted]%). The pre-PBAC response argued that this respecified analysis used a demonstrably unrealistic rate of disease progression in the natural history arm, and a treatment effect which is lower than what was observed in the randomised phase of APPEAR-C3G, and utility values applied did not reflect the C3G population as they were based on an elderly general CKD population.

6.86 The results of a scenario analysis assessing the cost-effectiveness of iptacopan compared to placebo in kidney transplant patients is summarised in Table 15. The submission assumed that this patient population would be identical to the native kidney population, with the exception of a more rapid decline in eGFR values in the placebo arm.

Table 15: Results of scenario analysis in a post-transplant population with disease recurrence

Analyses	Incremental cost	Incremental QALYs	ICER
Assume a post-transplant population with annual change in placebo arm based on time between disease recurrence and graft failure in the Halfon 2025 publication (-23.0 mL/min/1.73 m^2 per year)	$[redacted][2]	3.3980	$[redacted][1]

Source: Table 3.44, pp211-213 of the submission
Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years
Note: During the evaluation the base case was respecified using a 5% discount rate, removing societal costs and correcting for errors in transplantation event costs and post-transplantation (graft failure) health state costs
The redacted values correspond to the following ranges:
[1] *$755,000 to < $855,000*
[2] *> $1,055,000*

6.87 Based on the scenario analysis, treatment with iptacopan was associated with an incremental cost per QALY gained of $755,000 to < $855,000 compared to placebo for the treatment of C3G in post-transplant patients who experience disease recurrence. This analysis was largely uninformative as there were no clinical data to inform a relative treatment effect between iptacopan and placebo in this population, the analysis relied on the assumption that patient characteristics between native kidney and post-transplant populations were identical, and failed to account for the risk of graft failure in iptacopan patients due to their prior transplantation.

Drug cost/patient/year

Table 16: Drug cost per patient for iptacopan

	APPEAR-C3G trial	Economic model	Financial estimates
Effective DPMQ, 56 × 200 mg capsules	-	$[redacted]	$[redacted]
Adherence	99.7%	100%	100%
Cost/patient/year	-	$[redacted] [a]	$[redacted] [a]
Continuing treatment criterion	None	None	89.5% at 6 months [b]
Treatment discontinuation	5.3% at 12 months	5.3% per year for 1.5 years then 1% per year thereafter [c]	5.3% per year for 1.5 years then 1% per year thereafter [c]

Source: constructed during the evaluation based on the Section 3 economic model and Section 4 budget impact model of the submission
Abbreviations: DPMQ, dispensed price maximum quantity; eGFR, estimated glomerular filtration rate
[a] Based on the effective DPMQ of $[redacted] per script × 13.0446 scripts per patient per year
[b] Based on the proportion of patients with a change in eGFR of ≤15 mL/min/1.73 m^2 at 6 months in the iptacopan arm of APPEAR-C3G (as a proxy for eGFR stabilisation)
[c] Based on 3/38 patients (7.89%) who discontinued during the APPEAR-C3G and B12001B extension study for the first 1.5 years and assumed for subsequent years

6.88 The inclusion of the continuing treatment criterion in the financial estimates was inconsistent with the key trial and economic model of the submission. The proposed continuing treatment restriction states that patients must have experienced clinical improvement or stabilisation of the condition, with no objective measures of response.

Estimated PBS usage & financial implications

6.89 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of iptacopan for the treatment of adults with C3G with either native kidneys or disease recurrence following a kidney transplant.

6.90 Table 17 presents the key inputs relied on in the financial estimates.

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incidence of C3G	1.0 per million. The submission noted published international estimates of C3G incidence ranging from 0.7 cases (Caravaca-Fontán 2023) to 2 cases per million (Medjeral-Thomas 2013). The incidence rate was applied to the Australian adult population and was assumed to remain constant over the initial 6 years of listing.	No Australian sources of C3G incidence were identified. There was a limited number of published studies assessing the incidence of C3G, and it is unclear whether the incidence of C3G has been accurately captured due to the rarity of the disease and changes in disease definitions over time. It is unclear whether the assumed incidence rate accounts for diagnosed cases among children (who would become eligible for treatment once they reach 18 years of age). The availability of a targeted treatment for C3G may increase the rate of C3G disease detection. DUSC considered this estimate appeared reasonable.

Parameter	Value applied and source	Comment
Prevalence of C3G	7.4 per million. Derived from an analysis of UK RaDaR registry data conducted in 2023 (Masoud et al., 2024). Among 287 patients who had an exact diagnosis recorded, 47% had C3G and 53% had IC-MPGN. The proportion with C3G was applied to the full cohort of 1,075 patients with MPGN (after deduction of deaths occurring prior to July 2022). The number of prevalent C3G patients was then estimated by dividing the number of patients with C3G by the UK overall population. The prevalence rate was applied to the Australian adult population and assumed to remain constant over the initial 6 years of listing.	No Australian sources of C3G prevalence were identified. The RaDaR registry analysis is likely to have underestimated the prevalence of C3G, as the registry does not include all diagnosed cases of C3G. It is unclear whether the assumed prevalence rate accounts for diagnosed cases among children (who would become eligible for treatment once they reach 18 years of age). The assumed prevalence of 7.4 cases per million appeared implausibly low in the context of the assumed incidence rate of 1 case per million. In general, there was a lack of large prevalence studies to allow accurate characterisation of C3G prevalence. The sponsor's clinical advisory board considered that prevalence is likely underrepresented in current datasets due to diagnostic barriers and poor coding. The PSCR revised the prevalence to 8.8 per million based on the modelled life-years in CKD1-3b health states. DUSC noted that the PSCR revised financial estimates included an additional prevalent population to account for children with C3G that turn 18 each year and become eligible for iptacopan. DUSC agreed this was an appropriate addition.
Proportion with/without a kidney transplant	11.1%/88.9%. Derived from a cross-sectional survey of nephrologists (N=195) managing patients with C3G (N=385) in France, Germany, Italy, Spain, the UK, the US, China, and Japan conducted from July 2022 to April 2023 (Sidhu et al., 2024). Among 189 patients in the EU, 21 (11.1%) had previously undergone a kidney transplant.	The publication reported the number of patients diagnosed with C3G who had received a kidney transplant; whereas the proposed restriction specifies patients who have experienced disease recurrence following a kidney transplant. The reported proportion for the EU was higher than the proportions reported for the US (2.0%; 2/100), China (3.3%; 2/60), Japan (0%; 0/45) and the overall proportion (6.5%; 25/385). However, the proportion was lower than the proportion of patients with a history of kidney transplant in the RaDaR registry analysis (31%; Masoud et al., 2024). The assumption of the same proportions for the incident and prevalent populations did not appear reasonable.
Grandfathered patients	[redacted][1] patients. The submission stated that at the time of the submission, [redacted][1] patients with C3G were receiving iptacopan under the sponsor's access program. Grandfathered patients were not added to the estimates to avoid double counting.	The 89.5% treatment response rate would not be applicable to grandfathered patients, as qualification for continuing treatment would have occurred in a previous year.

Parameter	Value applied and source	Comment
Uptake rate	Yr 1: 50%; Yr 2: 60%; Yr 3: 70%; Yr 4 to 6: 80%. The submission argued that uptake of iptacopan is likely to be high, due to the oral route of administration and the lack of other targeted treatment options for C3G. The same uptake rates were assumed for patients with native versus transplanted kidneys, and incident versus prevalent patients.	The evaluation considered uptake rates were uncertain. Eligible prevalent patients and incident patients with native kidneys not electing treatment each year were assumed to remain eligible in subsequent years, with the uptake rate corresponding to the subsequent year used to derive the number of initiating patients. This resulted in very high overall uptake. It is unclear whether uptake will be the same among patients in the incident and prevalent populations. DUSC considered that these rates may be underestimated given the absence of other treatment options.
Continuation rate in first treatment year	Treatment response was based on the proportion of patients with a ≤15 mL/min/1.73 m^2 change in eGFR at 6 months in the iptacopan arm of the APPEAR-C3G trial (89.5%). The submission assumed that all initiating patients would receive treatment over the 24-week initial treatment phase, and that 89.5% of initiating patients would continue treatment for the remainder of the first treatment year.	As no specific outcome measures are included in the proposed continuing treatment restriction (patients must have experienced clinical improvement or stabilisation of the condition), DUSC agreed with the evaluation that it is unclear whether the assumed continuation rate will be observed in clinical practice. Additionally, patients/clinicians may be reluctant to discontinue treatment if there is a perceived benefit associated with ongoing treatment (i.e., slowing of disease progression).
Treatment persistence (patients remaining on treatment at the start of each year)	Yr 1: 100.0%; Yr 2: 94.87%; Yr 3: 91.95%; Yr 4: 91.03%; Yr 5: 90.13%; Yr 6: 89.23%. The submission stated that the treatment discontinuation rate for the initial 18 months was based on the number of discontinuations in the iptacopan arm of the APPEAR-C3G trial (3/38; 7.89%). Beyond 18 months, an annual discontinuation rate of 1.0% was assumed. Persistence was assumed to be the same for patients with native and transplanted kidneys.	The evaluation considered the assumed discontinuation rates were uncertain. The follow-up duration of 18 months could not be validated based on data presented in the submission. The proposed restriction states that patients must discontinue treatment prior to dialysis or kidney transplantation. It is unclear whether the assumed discontinuation rates accounted for discontinuations due to dialysis, transplantation or deaths. DUSC noted the lack of long-term data regarding trajectories of treated patients and considered this estimate was uncertain.
Treatment adherence	100%; assumption.	DUSC considered that whilst adherence would be high in this patient group, it agreed with the evaluation that 100% adherence is unlikely.

Source: Section 4, pp214-238 of the submission; Section 4 financial implications Excel workbook
Abbreviations: C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; EU, European Union; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; RaDaR, National Registry of Rare Kidney Diseases; UK, United Kingdom; Yr, Year
The redacted values correspond to the following ranges:
[1] *< 500*

6.91 Table 18 presents the estimated use and financial implications of listing iptacopan on the PBS for the treatment of C3G as presented in the submission and the revised estimates from the PSCR. The revisions to the financial estimates were substantial and complex, including changes to the approach used to estimate the size of various eligible populations, which were not validated. DUSC noted that there was also an error in the updated first year script numbers, which was corrected in the below values.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Total initiating patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total continuing patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of iptacopan						
Net cost to the PBS/RPBS	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]
Cost to the MBS [b]	$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]
Estimated use and financial implications, revised in the PSCR						
Total initiating patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total continuing patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed (corrected) [a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to the PBS/RPBS (corrected)	$[redacted][4]	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][8]	$[redacted][8]
Cost to the MBS [b]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to PBS/RPBS/MBS (corrected)	$[redacted][4]	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][8]	$[redacted][8]

Source: Table 4.14, pp227-228; Table 4.16, pp229; Table 4.20, p236 of the submission; Section 4 financial implications Excel workbook.
[a] Assuming 6.00 initial scripts and 7.04 continuing treatment scripts per patient in the first year of treatment, and 13.04 continuing treatment scripts per patient in subsequent years
[b] Includes costs associated with an increase in professional attendances (MBS Item 411) and cost offsets associated with dialysis (MBS Items 13100, 13103, 13104, 13105, 13109) and kidney transplant (MBS Items 36506, 36509, 36503). Some of the assumed MBS cost offsets were omitted from the total MBS costs in the financial implications Excel workbook
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] *$20 million to < $30 million*
[6] *$30 million to < $40 million*
[7] *$40 million to < $50 million*
[8] *$50 million to < $60 million*

6.92 The submission estimated cost to the PBS/RPBS was $10 million to < $20 million in Year 1, increasing to $40 million to < $50 million in Year 6, a total cost of $100 million to < $200 million over the initial 6 years of listing. The corrected PSCR estimates resulted in a cost to the PBS/RPBS of $10 million to < $20 million in Year 1, increasing to $50 million to < $60 million in Year 6, a total cost to the PBS/RPBS of $200 million to < $300 million, primarily due to a larger prevalent population.

6.93 The estimated cost to the PBS/RPBS/MBS was considered uncertain due to the following reasons:

- No studies reporting the prevalence and incidence of C3G in Australia were identified, and there was a limited number of published international studies assessing the prevalence and incidence of C3G. The assumed prevalence of 7.4 cases per million (derived from an analysis of the UK RaDaR registry) appeared implausibly low in the context of the assumed incidence rate of 1 case per million, implying a disease duration of approximately 7 years. This is also substantially lower than the modelled

disease duration of 43 years in the placebo arm of the economic model. The estimated cost to the PBS/RPBS was highly sensitive to the assumed incidence and prevalence of C3G. The prevalence was updated to 8.8 cases per million in the PSCR, based on modelled outcomes.

- The numbers of prevalent and incident patients were derived by applying the assumed prevalence and incidence rates to the Australian adult population. However, this approach did not appear to account for diagnosed cases among children (who will become eligible for treatment once they reach 18 years of age). DUSC noted that this paediatric population was included in the revised estimates provided in the PSCR, and considered that was appropriate.
- The assumed uptake rates were considered uncertain. Eligible prevalent patients and incident patients with native kidneys not electing treatment each year were assumed to remain eligible in subsequent years, resulting in very high overall uptake. It is unclear whether uptake will be the same among patients in the incident and prevalent populations.
- There is a risk of use outside of the proposed restriction among patients with Stage 4 to 5 CKD and patients with a UPCR < 1.0 g/g. DUSC agreed but noted that this risk was low given the proposed system for controlled access.
- The submission assumed that all eligible prevalent patients, and eligible incident patients with native kidneys would remain eligible for treatment in subsequent years. However, not all patients will continue to meet the eligibility criteria in subsequent years (e.g., CKD Stage 1 to 3b disease). Conversely, some patients not meeting specific eligibility criteria in the initial year (e.g., UPCR ≥1.0 g/g or 113 mg/mmol) may meet the criteria in a subsequent year.
- The proposed continuing treatment restriction states that patients must have experienced clinical improvement or stabilisation of the condition to qualify for continuing treatment. However, no specific outcome measures are included in the proposed restriction, and it is unclear whether the assumed continuation rate (89.5%) will be observed in clinical practice. Patients/clinicians may be reluctant to discontinue treatment with iptacopan if there is a perceived benefit associated with ongoing treatment (i.e., slowing of disease progression).
- The submission assumed perfect treatment adherence, which is unlikely to occur in clinical practice.

6.94 Table 19 presents the results of sensitivity analyses presented in the submission and conducted during the evaluation.

Table 19: Sensitivity analyses presented in the submission and conducted during the evaluation

	Estimated cost over 6 years
Base case (cost to PBS/RPBS)	$ [redacted][1]
C3G incidence (base case: 1.0 per million)	
0.66 per million (Caravaca-Fontan 2023)	$ [redacted][1]
1.3 per million (Sutherland 2020)	$ [redacted][1]
2.0 per million (Medjeral-Thomas 2013)	$ [redacted][2]
C3G prevalence (base case: 7.4 per million)	
5 per million [a]	$ [redacted][1]
12.8 per million	$ [redacted][2]
20 per million [a]	$ [redacted][3]
40 per million [a]	$ [redacted][4]
Proposed population (baseline: patients ≥18 years with native kidney or disease recurrence post-transplant)	
Native kidney only	$ [redacted][1]
Include patients aged 12 to 17 years	$ [redacted][1]
Proportion achieving treatment response (base case: 89.5%)	
Decrease to 80%	$ [redacted][1]
Increase to 100%	$ [redacted][1]
Treatment discontinuation rate (base case: 5.26% per year for initial 18 months; 1.00% per year thereafter)	
5.26% per year in all years	$ [redacted][1]
Discontinuations removed	$ [redacted][1]

Source: Constructed during the evaluation using the Section 4 financial implications Excel workbook
Abbreviations: C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; Y, Year
[a] Smith et al. (2019) reported prevalence rates ranging from 5 per million to 140 per million
[b] Derived based on a 10% absolute increase or decrease in uptake across all years
The redacted values correspond to the following ranges:
[1] $100 million to < $200 million
[2] $200 million to < $300 million
[3] $300 million to < $400 million
[4] $700 million to < $800 million

6.95 The estimated cost to the PBS/RPBS was highly sensitive to the assumed incidence and prevalence of C3G.

Quality Use of Medicines

6.96 The submission proposed the following activities to support the quality use of medicines:

- Targeted educational materials for nephrologists, focusing on appropriate patient selection criteria, diagnostic confirmation of C3G, baseline assessments, and ongoing monitoring protocols.
- A controlled access scheme to ensure iptacopan is only dispensed through specialised nephrology centres.
- Development of a patient safety card and a patient/caregiver guide to promote treatment adherence and early identification of potential adverse events.
- An annual reminder of mandatory revaccinations to mitigate the risk of infections caused by encapsulated bacteria.

Financial Management – Risk Sharing Arrangements

6.97 The submission did not propose a risk-sharing arrangement.

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

7 PBAC Outcome

7.1 The PBAC did not recommend iptacopan for treatment of complement 3 glomerulopathy (C3G). The PBAC considered that there is a high clinical need for treatments for C3G, which is a condition that impacts relatively young patients and causes decline in kidney function. The PBAC considered it is possible that iptacopan provides a clinical benefit for some patients in terms of slowing progression to end-stage kidney disease. However, the PBAC noted the clinical benefit was not sufficiently supported as the trial only demonstrated statistically significant improvement in the surrogate outcome of change in proteinuria, with no significant difference in eGFR. The PBAC considered that the modelled outcomes relating to avoidance of long-term dialysis and transplant were improbable and highly uncertain due to the limited clinical data, reliance on surrogate outcomes, and unsupported assumptions in the economic model. The PBAC considered that the cost-effectiveness of iptacopan had not been established as the ICER was extremely high at the requested price despite optimistic inputs to the economic model.

7.2 The PBAC considered that the primary reason for this outcome was the comparative clinical evidence.

7.3 The PBAC acknowledged the impact of C3G on individuals who are often children or young adults, working, and raising or starting families. Input from individuals, healthcare professionals and organisations highlighted symptoms of end stage kidney disease frequently require healthcare visits or hospitalisation and impact their ability to attend school and work, causing significant carer burden. The input from individuals with C3G noted the impact of chronic kidney disease, relapses and treatment burden on their ability to participate in daily activities and their mental health. 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.

7.4 The PBAC noted the proposed clinical place for iptacopan was as an add-on to background therapy with an ACEI/ARB, with or without corticosteroids and/or mycophenolate mofetil in patients with native kidneys, and as an add-on to standard immunosuppressive regimens in patients with disease recurrence following a kidney transplant. The PBAC considered that the proposed clinical place was appropriate.

7.5 The PBAC noted that the submission requested that the PBAC consider extending the restriction to include adolescents aged 12 to 17 years, although the TGA indication is limited to adults and no data were presented for this population. The PBAC noted that the ongoing APPEAR-C3G trial (expected completion in 2026) will include results for the adolescent cohort. The PBAC noted that disease progression is faster among adult

patients diagnosed with C3G compared with younger patients[1] and therefore the clinical evidence and magnitude of effect may not be directly comparable between adult and adolescent patients. The PBAC considered in the absence of evidence of safety and effectiveness in adolescent patients it would be reasonable for the listing to be limited to adult patients, but additional evidence in the adolescent population may support a broader age range.

7.6 The PBAC noted that the submission proposed listings for patients with native kidneys and for those who have received kidney transplants with disease recurrence, however no comparative data were available in post-transplant patients. The PBAC considered that there is a high unmet need in the small group of post-transplant patients and that although there were no comparative data, the single-arm studies suggested iptacopan was associated with statistically significant reduction in C3 Deposit Score at 12 weeks from baseline, and it was biologically plausible that it would be similarly effective in these patients as it is in patients with native kidneys. The PBAC noted the proposed criteria for initiation for post-transplant recurrence of C3G were broader than those for native kidney initiation and considered that they should be aligned with the criteria proposed for native kidney initiation in terms of eGFR and UPCR. The PBAC also considered that post-transplant patients should be allowed to initiate iptacopan treatment for recurrent C3G at any point in time.

7.7 The PBAC considered that the proposed Authority levels for the listings were appropriate (written Authority for initial treatment and streamlined for continuing treatment). The PBAC also considered that treatment should be initiated by a nephrologist and that nurse practitioner prescribing was not appropriate in this indication. The PBAC considered that ongoing monitoring of C3G patients was required and 60-day prescribing of iptacopan was not appropriate at this time.

7.8 The PBAC considered the nominated main comparator of "standard of care" was appropriate, and noted that pegcetacoplan is a relevant near-market comparator. This submission did not present an indirect comparison with pegcetacoplan given limited published data for the key trial of pegcetacoplan, VALIANT.

7.9 The PBAC noted that the submission was based on a head-to-head randomised trial of iptacopan versus placebo in patients with C3G who have native kidneys (APPEAR-C3G), with additional supportive evidence from a single-arm study of iptacopan in adult patients with C3G who have native kidneys or recurrent C3G following a kidney transplant (X2202); and a long-term extension study of iptacopan (B12001B) in the subset of patients who rolled over from the APPEAR-C3G trial and the X2202 phase 2

[1] C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy, Kidney International (2018) 93, 977-985

study. The PBAC noted the outcomes in the key trial and supportive studies were primarily based on short-term changes in proteinuria and eGFR, noting that the comparative data were limited to 6 months, after which patients crossed over to iptacopan. The submission also 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. The PBAC agreed with the ESC that biological plausibility and epidemiological evidence support proteinuria and eGFR levels as prognostic variables for kidney disease progression, however, the magnitude by which proteinuria reduction or eGFR stabilisation mitigates progression to ESKD and its associated sequelae remains uncertain.

7.10 The PBAC noted that in APPEAR-C3G treatment with iptacopan was associated with a statistically significant reduction in 24-hour UPCR compared to placebo at 6 months from baseline, and effects on proteinuria were sustained at 12 months during the open-label extension period and up to 24 months in the B12001B long-term extension study. However, the PBAC noted that although treatment with iptacopan was associated with a numerical improvement in eGFR compared to placebo at 6 months, the result did not achieve statistical significance. Longer-term follow-up in patients originally randomised to the iptacopan arm appeared to show a decline in eGFR but may have been impacted by outlier values and the small number of patients included in the analysis. In patients originally randomised to placebo and subsequently switched to iptacopan, eGFR remained stable throughout the trial and extension period. The PBAC noted that no changes in QoL were demonstrated in the comparative phase of the APPEAR-C3G study.

7.11 The PBAC also noted an exploratory analysis of the rate of change in eGFR (slope per year) was conducted by pooling data from the APPEAR-C3G, X2202 and B12001B studies (but using the native kidney cohort of X2202 only) including historical estimates collected for approximately 2 years prior to entry into APPEAR-C3G and X2202. This analysis also informed the economic evaluation of iptacopan. The PBAC considered that this pooled analysis was unreliable due to heterogeneity between the included studies in terms of study design, duration and populations, and due to methodological limitations (pooling of data from non-parallel observation periods) and was subject to potential confounding due to substantial differences in use of supportive therapies during the pre- and post-randomisation periods of the analysis. The PBAC considered that the evidence provided did not support a difference in eGFR in patients treated with iptacopan, acknowledging that this may be due to the short duration of the comparative phase of the trial. Overall, the PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data as it was based on short-term biomarkers (proteinuria reduction), with no

demonstrated difference in terms of change in eGFR compared to placebo and no long-term data demonstrating the effect on progression to ESKD.

7.12 The PBAC noted that iptacopan was associated with a higher rate of adverse events compared with placebo, and an increased risk of serious adverse events. 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. Overall, the PBAC considered the claim of inferior comparative safety was reasonable. The PBAC noted that the draft product information for iptacopan included 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 iptacopan 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 iptacopan for a condition specified under the Pharmaceutical Benefits Scheme (PBS).

7.13 The submission presented a stepped cost-utility analysis for the economic evaluation of iptacopan compared to placebo. The PBAC noted the ESC advice that the model structure was similar to other published models in chronic kidney disease, however the cost-effectiveness estimate should not be considered reliable as the model was built around a difference in eGFR decline between treatment arms which was not supported by the key randomised trial for iptacopan, which did not demonstrate a statistically significant improvement eGFR between treatment arms. The PBAC noted that the change in eGFR over time in the iptacopan arm was based on the assumption that treatment would prevent all C3G-mediated changes in kidney function, with treated patients assumed to have the same eGFR decline as prospective living kidney donors registered at UK renal treatment centres between 2003-2015 (Fenton 2018). The PBAC considered that this assumption was optimistic and not supported by the trial data. In addition, the submission estimated the change in eGFR over time in the placebo arm based on the mean change in eGFR per year using data reported in the pre-iptacopan period from the pooled analysis of APPEAR-C3G, X2202, B12001B studies. As noted above (7.11) the PBAC considered this analysis unreliable. Overall, the PBAC acknowledged that, given the limited duration of comparative data, it is difficult to determine the most appropriate inputs for eGFR over time, but considered that the submission's chosen approach was optimistic and likely to substantially overestimate the treatment benefit for iptacopan.

7.14 The PBAC noted that utility values were also a major driver of the modelled benefit for iptacopan. The PBAC noted that neither utility values from the source used in the submission (EQ-5D-5L from the general public for PH1 health states (de Freitas 2023)) nor the alternative values (from an Australian cost of illness study for chronic kidney disease (Deloitte 2023)) reflected the C3G population. The PBAC considered that the utility values used in the submission appeared extremely low and agreed with the ESC that values from CKD patients were more likely to reflect the impact of dialysis and graft failure on QoL in patients with C3G.

7.15 The PBAC noted that the base case ICER was $955,000 to < $1,055,000 per QALY gained and this was reduced to $755,000 to < $855,000 when productivity costs were included, reflecting the impact of C3G on young patients. The PBAC also noted that the ICER increased substantially (up to > $1,055,000 per QALY) with multivariate analyses, demonstrating that the estimated cost per QALY gained with iptacopan compared to placebo was highly uncertain and could be substantially higher than estimated in the base case. The PBAC noted the pre-PBAC response comments that the ESC respecified base case was overly conservative and not reflective of the treatment effect in the trial or the utility values of the relevant population, but considered that the base case was overly optimistic. The PBAC considered that the cost-effectiveness of iptacopan had not been established as the ICER was very high at the requested price despite optimistic inputs to the economic model.

7.16 The PBAC recalled that it had considered several previous economic models representing progression to ESKD in various indications and considered 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. The PBAC considered that the very high ICERs from the submission model reflect the very high price requested for iptacopan and advised that a price reduction for iptacopan would be required to bring the ICER into a range to be considered cost-effective. The PBAC noted the sponsor's suggestion in the pre-PBAC response regarding the cost per patient accepted for lumasiran but considered there were substantial differences in the disease course and impacts on patient QoL between C3G and PH1 and a similar approach was not reasonable for C3G.

7.17 The PBAC noted that the estimated financial impact of listing iptacopan was sensitive to the incidence and prevalence of C3G in Australia, which are uncertain, with limited data to inform these values. The PBAC considered that the estimated prevalence of 8.8 per million appeared reasonable, but noted that other sources (Smith et al. 2019) suggest that prevalence may be substantially higher. The PBAC also considered that the discontinuation rate was unclear as it was unlikely that the trial discontinuation rate would apply in the longer term. The PBAC also considered that it was unclear whether the restriction criterion limiting continuing treatment to patients with a response to treatment would result in patients discontinuing treatment, as there were no specific measures proposed. Given the high level of uncertainty in the size of the population and the duration of treatment, the PBAC considered a risk-sharing arrangement would likely be required, to address the risk of use in a much larger population than expected, or for longer than expected.

7.18 The PBAC considered a resubmission for iptacopan should include a revised economic model using a more conservative approach to estimating the long-term benefits from iptacopan (as per paragraph 7.13), and resulting in a lower ICER (as per paragraph 7.15). The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.19 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

9 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.

10 Sponsor's Comment

Novartis is disappointed with the PBAC's decision not to recommend iptacopan (Fabhalta®) for C3G. While we welcome the PBAC's acknowledgment of the significant burden and unmet need, C3G is an ultra-rare disease that typically affects younger people and leads to progressive kidney decline, making it critical that the value of iptacopan (Fabhalta®) is appropriately recognised for Australian patients and the healthcare system.

At this time, pursuit of a PBS listing does not appear to be viable. However, we remain committed to supporting Australian C3G patients and plan to provide access through alternative pathways where possible.

We sincerely thank patients, clinicians, and organisations for their valuable contributions to the PBAC process.