NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Pegcetacoplan for treating complement 3 glomerulopathy or primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pegcetacoplan in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: March 2026

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using pegcetacoplan in the NHS in England.

For further details, see NICE's technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

- Closing date for comments: 7 April 2026
- Second evaluation committee meeting: 23 April 2026
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Pegcetacoplan should not be used to treat complement 3 glomerulopathy or primary immune-complex membranoproliferative glomerulonephritis in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with pegcetacoplan that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

What this means in practice

Pegcetacoplan is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that pegcetacoplan is value for money in this population.

Why the committee made these recommendations

Usual treatment aims to control the symptoms of complement 3 glomerulopathy or primary immune-complex membranoproliferative glomerulonephritis. Pegcetacoplan aims to treat the underlying condition.

Clinical trial evidence shows that pegcetacoplan reduces protein in the urine and slows the decline of kidney function compared with placebo.

There are uncertainties in the economic model, including:

- how stable disease is defined and used in the model

- how it includes the costs and benefits of avoiding a kidney transplant.

Because of the uncertainties in the economic model it is not possible to determine the most likely cost-effectiveness estimate for pegcetacoplan. But it is likely to be above the range that NICE considers an acceptable use of NHS resources. So, pegcetacoplan should not be used.

2 Information about pegcetacoplan

Anticipated marketing authorisation indication

2.1 Pegcetacoplan (Aspaveli, Sobi) does not have a marketing authorisation in the UK yet. The Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending the granting of a marketing authorisation for the medicinal product pegcetacoplan, intended for treating C3 glomerulopathy or primary immune-complex membranoproliferative glomerulonephritis.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for pegcetacoplan.

Price

2.3 The list price for pegcetacoplan is £3,100 per 1,080 mg/20 ml vial (excluding VAT; sourced from company submission).

2.4 The company has a commercial arrangement. This makes pegcetacoplan available to the NHS with a discount and it would have also applied to this indication if pegcetacoplan had been recommended. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for SOBI will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by SOBI, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The conditions

3.1 Complement 3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) are rare and debilitating glomerular conditions. They primarily affect children and young people. They are distinct conditions, but both caused by overactive complement systems that result in excessive C3 protein in the kidneys. This leads to progressive decline in kidney function and irreversible kidney damage. Common symptoms include blood in the urine (haematuria), high levels of protein in the urine (proteinuria), reduced amounts of urine and swelling in many areas of the body. The kidney damage often leads to kidney failure, requiring dialysis and kidney transplants. The patient experts emphasised the psychological impact of knowing that kidney function will eventually deteriorate to the point of needing dialysis and transplantation. They explained that this impact increases as the condition worsens. And they explained how after a transplant, the conditions frequently recur and progress again, often requiring further dialysis and transplants. The patient experts explained the many physical and mental challenges of living with or caring for someone with these conditions. They described the impact it can have on all aspects of life such as school, work and relationships. It also has an impact on families and carers. They also noted that diagnosing C3G and IC-MPGN is challenging and can take a long time. The diagnosis is confirmed through urinalysis, serology and biopsy, with immunofluorescence used to differentiate between the conditions. The patient experts also noted there is a lack of knowledge and awareness of the conditions. The committee acknowledged the substantial burden and impact on quality of life that C3G and IC-MPGN has on people living with the condition, their carers and families. It

concluded there is a significant unmet need for effective treatments for these conditions.

The treatment pathway

3.2 There are no NICE-recommended treatments for C3G or IC-MPGN and no defined clinical pathways. Usual care is treatments to reduce proteinuria, manage hypertension and reduce inflammation. These include angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), and immunosuppressants including corticosteroids. Treatment decisions are informed by guidelines from the National Renal Complement Therapeutics Centre and Kidney Disease Improving Global Outcomes (KDIGO). Mycophenolate mofetil (MMF) plus corticosteroids (in addition to ACE inhibitors or ARBs) may be used for moderate to severe symptoms. Off-label eculizumab is also commissioned by NHS England for treating recurrent C3G after a transplant in people with a significant decline in kidney function. This is defined as a more than 20% decline in estimated glomerular filtration rate (eGFR) within the previous 3 months. The patient and clinical experts emphasised the unmet need for a treatment for C3G and IP-MPGN that stops or slows down the progression of chronic kidney disease (CKD). They reiterated that current available treatments only deal with symptoms. The committee agreed there is a significant unmet need for an effective treatment that targets the underlying condition and delays progression. The committee understood that the treatment pathway may need formalising if a new treatment for C3G were to be recommended.

Comparators

3.3 The comparators in NICE's final scope included established clinical management without pegcetacoplan, and eculizumab for highly aggressive C3G recurrence after a kidney transplant. Established clinical management included ACE inhibitors, ARBs, corticosteroids, MMF and sodium–glucose cotransporter-2 (SGLT2) inhibitors. The company's submission compared pegcetacoplan plus standard care with standard

care alone. But it did not include a comparison of eculizumab with pegcetacoplan for treating highly aggressive C3G recurrence after a kidney transplant. The company stated that eculizumab was not a relevant comparator because it is not in widespread use in UK practice, and that there is a lack of data to show its effectiveness in stabilising the conditions. The clinical experts noted that eculizumab is rarely used in practice and only used for a very aggressive, rapid form of recurrence. One expert noted that 1 patient each year would use eculizumab, and perhaps fewer than this. When there is aggressive recurrence the clinical experts would likely offer eculizumab until the condition stabilised, then offer pegcetacoplan. The committee noted that a comparison between pegcetacoplan and eculizumab could have been informative. But it understood eculizumab, if used, would be at a point in the treatment pathway when pegcetacoplan is unlikely to be used. So, the committee concluded that standard of care is the appropriate comparator.

Clinical effectiveness

3.4 The company's submission included evidence from 4 clinical trials: a phase 3 randomised controlled trial (VALIANT) and its longer-term extension study (VALE), and two phase 2 studies (NOBLE and DISCOVERY). The key trial, VALIANT (n = 124), was a double-blind study in 122 locations including 9 UK sites. It included people aged 12 years and above with either C3G (n=96) or primary IC-MPGN (n=28) who had an eGFR of at least 30 ml/min/1.73 m^2. It compared pegcetacoplan with placebo over 26 weeks, before entering an open-label phase in which all participants had pegcetacoplan for a further 26 weeks. The treatment regimen was given on an ongoing basis throughout the study. Pre-existing standard of care was also provided in both arms. The primary outcome was reduction in proteinuria at 26 weeks compared with baseline. The pegcetacoplan group showed a statistically significant reduction from baseline proteinuria compared with the placebo group (relative reduction 68.1%, 95% confidence interval 57.3 to 76.2). The pegcetacoplan group showed similar improvements over placebo in secondary outcomes

including eGFR stabilisation, C3 staining and change in C3G histological index score. The committee concluded that pegcetacoplan plus standard of care showed improvements over placebo plus standard of care.

Population

3.5 The proposed population in the company's submission for pegcetacoplan is people aged 12 years and above with C3G or IC-MPGN. This is in line with the proposed marketing authorisation, and the marketing authorisation granted by the European Commission. VALIANT excluded people who had an eGFR below 30 ml/min/1.73 m^2, which corresponds with CKD stages 4 and 5. The company said that CKD stages 4 and 5 are often excluded from trials, but it provided data for a small subgroup of 3 people in VALIANT (3.23% of the trial population) who progressed to CKD stage 4 after trial screening. One person was randomised to the pegcetacoplan arm and the other 2 had placebo. The company said that this subgroup showed favourable outcomes for pegcetacoplan compared with placebo but acknowledged the sample size was small. The EAG emphasised there was a lack of data showing the effectiveness of pegcetacoplan in people with CKD stages 4 and 5. The clinical experts stated that CKD stage 4 encompasses a wide range of disease, with eGFR ranging from 15 to 29 ml/min/1.73 m^2. They explained there is a distinction between a CKD stage as a chronic state that is maintained over a period of time, and situations when the eGFR is in the relevant range for only a short period because of acute disease. They also explained that treatment decisions are based on several clinical parameters. They would consider use of pegcetacoplan in CKD stage 4. But they would be less likely to use pegcetacoplan in CKD stage 5, because of the extent of kidney damage. So, including an eGFR cut-off in a NICE recommendation would not be useful for clinicians. The committee asked whether there would be any additional data for CKD stages 4 and 5 in the future. The company said that in the current compassionate use programme, 10% of people had stage 4 CKD. It also advised that a phase 4 real-world study is starting soon with a follow up of 7 years, but the

results will not be available for this evaluation. The committee acknowledged the lack of evidence in the CKD stage 4 and 5 population. But it agreed that it would not be appropriate to restrict any recommendation, because several clinical parameters are used when considering use of pegcetacoplan. So, the committee concluded that any recommendation would be for the population in line with the proposed marketing authorisation for pegcetacoplan.

Treatment-effect waning

3.6 The company did not model treatment-effect waning in its base case. It stated that treatment-waning analyses were not appropriate because the effectiveness of pegcetacoplan is not expected to reduce over time. The EAG advised it was not possible to observe treatment-effect waning over time, because of short follow-up duration in the clinical trials. It noted that people initially randomised to pegcetacoplan in VALIANT showed gradual deterioration in secondary outcomes (such as eGFR) between 26 and 52 weeks. The EAG suggested that further exploration of treatment-effect waning in the long term might be informative for the committee. The company provided an updated analysis from VALE showing mean change from a realigned baseline of eGFR for all patients combined. This assumed that baseline for the placebo group was the last available non-missing assessment before starting pegcetacoplan. The updated analysis showed no waning effect up to week 100. The clinical experts advised there is no biological rationale for pegcetacoplan's effectiveness to reduce over time. But there may be some decline if kidney damage had occurred before starting pegcetacoplan. The committee concluded that assuming no treatment-effect waning is reasonable but uncertain because of the lack of data. The committee would welcome a treatment-effect waning scenario if further data becomes available.

Baseline C3 protein

3.7 The company's submission included subgroup analyses based on the condition, age, baseline C3 protein level and transplant status. The EAG noted that pegcetacoplan appears less effective in the subgroup with normal C3 protein baseline levels compared with low baseline levels. At 26 weeks, there were statistically significant differences in change in proteinuria and eGFR from baseline between the low-baseline C3 subgroup compared with the normal-baseline C3 subgroup (-78.23 compared with -42.76, p=0.0003). The EAG suggested this could mean baseline C3 is a treatment-effect modifier, and that cost-effectiveness analyses based this subgroup would be informative. The company noted that VALIANT was not statistically powered to analyse these subgroups and it would be inappropriate to use the analysis to inform treatment. The clinical experts agreed, stating they would not want to exclude consideration of pegcetacoplan based solely on C3 levels. They would use a range of clinical parameters when deciding on treatment options. Based on the limited data available, and that other clinical parameters are also important to consider, the committee concluded that a subgroup analysis based on C3 protein level was not appropriate for decision-making.

The company's model

UPCR health states

3.8 The company provided a cohort-level state-transition (Markov) model that aimed to capture the progression of CKD through to end-stage disease, dialysis (peritoneal dialysis and haemodialysis) and kidney transplantation. The model compared pegcetacoplan plus standard care with standard care alone. It included 3 health states based on the urine protein-to-creatinine ratio (UPCR; below 1, 1 to 3 and above 3) and 1 health state for 'stable disease'. Each of these 4 health states were further stratified into the 5 CKD stages. Additional health states for dialysis, transplant and death were also included. Duplicate health states were

used for before and after a transplant, with the exception that the pre-transplant state also included separate dialysis states for people who could not have a transplant. In total, 49 health states were used in the model. The EAG advised that the company's model was complex and previous NICE appraisals of kidney disease used simpler structures, such as models without UPCR states. It stated the more complex model structure may be reasonable, but exploring a more simplistic model could be useful. It also noted that the model validation provided by the company was insufficient and it would like to see further evidence, including cross-validation of the model assumptions and inputs against all relevant technology appraisals. The committee acknowledged the model was complex and noted that the validation provided was not sufficient. But it concluded that the UPCR health states correlated with important clinical and cost outcomes.

Stable-disease health state

3.9 The company defined stable disease as having a UPCR of less than 0.5 g/g. In the model, the proportion of people who transition to the stable-disease state was informed by the number of people in VALIANT who met this definition at the end of follow up. People in the stable-disease state are assumed to stop treatment with pegcetacoplan until disease relapse. Because of the limited trial duration of VALIANT, long-term data for how long participants had stable disease was not available. So, the company based disease relapse on a Spanish retrospective cohort study in 97 people with C3G (Caravaca-Fontán et al. 2020). For each 3-month cycle, the model applied a constant relapse rate of 7.76% across all arms, informed by the 26-month median relapse duration from Caravaca-Fontán. The committee noted that stopping pegcetacoplan in this way was not permitted in VALIANT. The company stated that inclusion of the stable-disease health state was informed by advice from clinical experts, who said people may stop pegcetacoplan when there is good disease control and restart it on disease relapse. The company explained that the model estimated that 50% of patients would be off treatment with

pegcetacoplan at 18 months. NICE's technical team advised that its requested analysis showed that in the company's base case, 50% of people are assumed to permanently stop pegcetacoplan treatment after 34 years. But this analysis also showed that the company's base case estimated total time spent on pegcetacoplan in the model as only 10.6 years (median). This showed the impact of including a stable-disease health state. The EAG stated that because the model already categorises by UPCR state, modelling a stable-disease state appears structurally redundant. There is also a lack of evidence to support remission or stopping treatment in people with C3G and IC-MPGN. The EAG advised that the assumptions related to the stable-disease state (the UPCR threshold, treatment discontinuation and duration of stable disease) have a substantial impact on the cost-effectiveness results. So, the EAG preferred to exclude a stable-disease state from its base case. This resulted in a large increase to the incremental cost-effectiveness ratio (ICER). The EAG also noted that the data informing transitions to UPCR of less than 0.5 g/g was based on small patient numbers from the trial. The company stated that the clinical evidence showed improvements in eGFR, but because the model assumed no eGFR improvement including a stable-disease state was appropriate to capture that benefit. The clinical experts at the committee meeting advised that they would cautiously consider stopping treatment in some instances, such as milder disease that had responded well to pegcetacoplan. They explained that stopping treatment would require monitoring for signs of disease progression. If disease activity returned, treatment would be restarted. They estimated that about 20% of people with C3G or IC-MPGN may have milder disease. The clinical experts said they would be more reluctant to stop treatment if someone had severe disease. The clinical experts also explained that any decision to stop treatment would be done after careful consideration and discussion between healthcare professionals, patients and their carers. They emphasised that some clinicians and patients would be reluctant to stop treatment with pegcetacoplan. The patient

experts stated they would be prepared to stop treatment if well enough and if their clinician believed that it was safe to do so, provided there was the option to restart treatment as soon as the disease progressed. Both the clinical and patient experts advised that stopping treatment was not a scenario they had experienced in practice, because there are no treatments that target the underlying condition. The committee noted that the key clinical trial did not allow stopping of pegcetacoplan in this way. Also, the modelling of any temporary stopping of treatment, and for how long treatment may be stopped, were highly uncertain. The committee decided that a much smaller number of people than estimated by the company's model may be able to temporarily stop treatment with pegcetacoplan. The committee noted the very high impact on the cost effectiveness estimates, in terms of:

- costs and health benefits
- assumptions about the definition of stable disease
- the modelling after stopping treatment
- both length of time for which treatment would stop and disease progression.

The committee concluded that a separate stable-disease state was not appropriate because it assumed that everyone in this health state would temporarily stop pegcetacoplan, which did not align with the views from clinical and patient experts. It also adds uncertainty to the model through estimating large quality-of-life gains, which was not justified by evidence. The committee would prefer to see an assumption that when UPCR is less than 1 with CKD stage 1, 20% of people would stop treatment temporarily, based on the clinical experts' estimate for mild disease. But the committee noted this figure was uncertain. So, it requested more analysis on the proportion of people who would temporarily stop treatment, the length of time for which treatment might be stopped and disease progression after stopping.

Kidney reallocation

3.10 The company's model included cost savings and quality-adjusted life year (QALY) gains from reallocating kidneys for transplants to other patients on the kidney transplant waiting list, because they were no longer needed by people having pegcetacoplan. The company used a queuing model, designed to analyse systems for access to limited resources, to assess the impact of 1 additional kidney on transplant waiting time. The queuing model was based on Zenois (1999), which the company explained is often used for modelling transplant medicines. Waiting list numbers, kidney supply and number of people on the transplant waiting list who died before having a transplant (NHS Organ and Tissue Donation and Transplantation Activity Report 2023/2024) were used in the model. The model estimated an average waiting time of 2.322 years. The company said this closely aligned to 2.18 years waiting time calculated directly from NHS data. To assess the impact of 1 additional kidney, the company reduced the number of new patients waiting for transplant by 1. The model estimated this would reduce the average waiting time to 2.318 years, translating to a reduced waiting time of 1.3 days. The company's base case applied this saving to the annual number of patients waiting for kidney transplant (3,043 patients), resulting in a cumulative saving of 10.65 years. The EAG stated that these cost savings and QALY benefits for people outside the C3G and IC-MPGN population are indirect effects that are not directly attributable to pegcetacoplan's impact on the treated population or their carers. It advised that this is outside the NICE reference case. So, the EAG excluded these costs and benefits from its base case. This resulted in a substantial increase in the ICER. The EAG noted that if kidney reallocation were to be captured in the model, this would raise methodological questions and concerns about how it should be included. For example, a queuing model is a population model. This is different to the main cost-effectiveness model, which models individual patients. The queuing model, or any other approach used to estimate kidney reallocation, would also need to be reviewed and validated by the

EAG alongside the cost-effectiveness model. The EAG also noted that cost savings and health benefits of reallocated kidneys were applied in the model from the start. It explained this would not be the case in practice because it would take several years before a kidney transplant would be required in the comparator arm of the model. The patient experts emphasised that many people with C3G or IC-MPGN are on the waiting list for kidneys, and some would still be on the waiting list if pegcetacoplan was made available, so people within the population could still benefit. This is because if a person on pegcetacoplan no longer needed a kidney, someone else within the population may benefit from that kidney instead. They also noted that the NHS kidney transplant waiting list is long, and people spend a long time waiting for a kidney. They emphasised it was important to consider the positive impacts of allowing more kidneys to be available to the NHS waiting list. The committee agreed there are benefits to the NHS from pegcetacoplan reducing the need for kidney transplants in people with C3G or IC-MPGN. It also noted that assumptions about stable disease (see section 3.9) had a large impact on the modelled treatment effectiveness of pegcetacoplan. The committee concluded that the benefits and costs related to kidney reallocation were outside of the NICE reference case for economic analysis because they were attributable to treating populations outside of the NICE scope for this evaluation. But it noted that non-reference case analysis may still be considered by a committee. The committee acknowledged that any non-reference case analysis on the impact of kidney transplant waiting lists would be inherently complex and uncertain because it is not driven by direct evidence. The committee considered the company's modelling approach and decided it was associated with methodological issues. These included using a population model to inform the cohort-based cost-effectiveness model, and applying reallocation benefits from the start of the model when it would take time for those benefits to be realised. So, the committee concluded that the company's approach was not suitable for decision making. But the committee emphasised that the benefits of

kidney reallocation are important to consider in its decision making as uncaptured benefits, which it took into account when determining an acceptable ICER.

Unequal follow-up data

3.11 In the company's model, the clinical-effectiveness estimates use 26-week follow-up data from VALIANT for the standard-care group. The pegcetacoplan group is informed by 52-week follow-up data, which includes the 26-week randomised controlled period and the open-label period. The EAG noted that using a longer observation period for pegcetacoplan could include further improvements or regression to the mean, which could lead to an exaggerated treatment effect. The EAG preferred to use the 26-week data for both groups. The company stated that it had used 52-week data to maximise available data and improve reliability of results. The company also provided a scenario analysis using 26-week VALIANT data in both arms. The EAG was unable to implement this scenario in the company's model, so the impact on the cost-effectiveness results is unknown. The committee agreed that both groups should use equal follow-up duration to reduce bias in the clinical-effectiveness results. So, using 26-week follow-up data would be most appropriate. The committee concluded that this should be implemented into the model in a way that is reproducible for the EAG.

Separate state-transition regression models for UPCR and eGFR

3.12 To inform the UPCR and eGFR state transitions and effectiveness, the company used 2 separate regression models. It noted that a combined regression model was not feasible because of limited trial follow-up data and sample size, which meant there were few transitions between the specific CKD stages. Instead, the company chose to model CKD progression using a constant eGFR slope. It stated this was consistent with clinical practice and NICE's evaluation of iptacopan for treating C3G (TA1102, terminated appraisal). The EAG emphasised that both regression models applied a treatment effect, which may mean any eGFR

treatment effect linked with UPCR improvements is counted twice. It also noted there were very wide standard errors for several UPCR transitions and low numbers of observations, resulting in poor validity. The EAG removed the treatment effect in the eGFR regression model, which had a large increase on the cost-effectiveness results. But the EAG said it would prefer a single regression that jointly modelled UPCR and eGFR, or a sequential model that uses UPCR as a predictor of eGFR. The company stated that it was already using a sequential approach in the modelling by using the modelled eGFR slope. The committee noted that the impact of this issue was increased because of the high number of health states in the company's model and that, given sufficient data, a single regression including coefficients for both UPCR and eGFR would be preferable. However, the committee agreed that a sequential model would be appropriate in this case (based on the evidence presented), and that the company had taken a sequential approach. So, it concluded the company's approach was acceptable for decision making.

Transition probabilities after kidney transplant

3.13 The company's model duplicates the health states before and after transplants. It also assumes that the transition probabilities after a transplant are the same as before transplant. The company said this assumption is because of limited post-transplant data in VALIANT and limited data in the literature, particularly for UPCR change. It noted that clinical feedback suggested transplanted kidneys deteriorate faster than native kidneys, because of lower baseline eGFR levels. But it was not possible to explore scenarios using different transition rates because of the current model structure. The company emphasised that if transplanted kidneys deteriorate faster this would likely favour pegcetacoplan, because more kidney transplants occur in the standard-care group. This makes the current model approach conservative. The clinical experts estimated that about half of all people who get a kidney transplant would not experience disease recurrence. The committee noted estimates from NHS England that disease would recur in about 80% of transplanted kidneys. The

company stated that this is not directly captured in the model. The committee also noted there are some people whose condition would progress quicker after transplant, and some whose disease would not progress at all. Neither of these situations are accounted for in the model. The committee acknowledged there is limited post-transplant data to inform the model but, because it does not assume a higher proportion of stable disease after transplant, the current model results may be conservative. So, the committee concluded that the current approach is uncertain but may be acceptable for decision making. Because of the uncertainty in how often disease would recur in post-transplant kidneys the committee would like to see more evidence on post-transplant outcomes, including the proportion of people whose disease would recur after transplant.

CKD utility values

3.14 The CKD stage 1 and 2 utility values in the company's model were informed by pooled VALIANT EQ-5D-5L data mapped to EQ-5D-3L. This was done using linear regression to assess the impact of covariates such as baseline EQ-5D, age and UPCR levels. The EAG stated that using pooled CKD stages 1 and 2 utilities misaligns with the model's separate UPCR and CKD-stage structure. It also had concerns that the linear regression did not account for repeated measures for each patient. It advised that a mixed model for repeated measure (MMRM) approach would be more appropriate. At clarification the company provided an MMRM model that appears to fit the trial data better than the linear regression model, but the results did not differ significantly. The company stated it was not able to incorporate the MMRM results for clarification, but can provide this information if needed. Utility values for CKD stages 3 to 5 were informed by Sidhu et al. (2024), with disutilities applied from VALIANT to people with elevated UPCR levels (more than 1 g/g). Dialysis utility values were informed by the literature from people with CKD having haemodialysis and peritoneal dialysis (Cooper et al. 2020). The EAG stated concerns about the literature-derived utility values for CKD stages

3 to 5. It preferred to align CDK stages 3 to 5 utility values with NICE's terminated technology appraisal of iptacopan for C3G (TA1102). The patient experts advised that CKD stages 1 to 3 are similar in terms of physical health, but CKD stage 3 would have more impact on school and work because it involves more appointments. They explained that CKD stages 4 and 5 have the biggest impact, with more physical symptoms such as fatigue and pain. This would further impact attendance at work or school, taking part in activities and socialising with peers. The patient experts added that having CKD stage 5 felt the same, or sometimes worse, than being on dialysis and that it involved a substantial treatment burden. The committee concluded that using VALIANT to inform utilities for CKD stages 1 and 2 was appropriate. But it would like to see results using an MMRM model because these take into account repeated measures and appear to better fit the data. It agreed with the patient experts that utility values for CKD stage 3 should be similar to CKD stage 1 and 2. And it expected to see a smaller decrease between CKD stages 2 and 3 than that used in the company's base case. So, the committee preferred to use the CKD stage 3 utility value applied in the EAG's base case. The committee concluded that applying the same utility values in CKD stage 4 to CKD stage 5 is unrealistic. So, the CKD stage 4 values should be amended to better reflect that disease stage, such as taking the midpoint between CKD stage 3 and 5.

Additional costs

3.15 The company assumed that the first dose of pegcetacoplan would be administered in clinic, with subsequent doses self-administered at no additional cost. It noted that it will fund a syringe system through a patient support programme. The EAG's clinical expert emphasised that although self-administration is an option, pegcetacoplan was administered in-centre during clinical trials. The clinical experts at the meeting said that some younger patients may continue to need some assistance, but this would already be accounted for in current care. The EAG advised that the company's approach is likely to underestimate administration costs, and

does not account for in-hospital administration for people who might be in hospital for other reasons. The company had excluded costs for vaccinations and antibiotics, but provided a scenario analysis at clarification that included these costs. The company acknowledged that vaccinations would be required before having pegcetacoplan and antibiotics are likely to be needed. The EAG's base case included cost of vaccination and antibiotics, which had minimal impact on the cost-effectiveness results. The company also included costs relating to cardiovascular events. The EAG emphasised that a direct effect on cardiovascular events was not observed in the trials, but acknowledged that the study length was limited. The EAG advised that pegcetacoplan's impact on cardiovascular events remained an uncertainty. The patient experts emphasised that cardiovascular events are common and they had personally experienced events including cardiac arrest and infective endocarditis. These can lead to extended hospital stays and impact on ongoing treatment, even delaying transplants. The clinical experts noted that the literature supports an elevated risk of cardiovascular events in this population, and that treatment interrupting disease progression would reduce that risk. The EAG also advised that biopsy costs were not included in the model, which may be required when confirming stable disease. It suggested that a scenario including cost of biopsy when entering the stable-disease state would be informative. The company was not able to address biopsy costs at clarification because of time constraints, but stated it would address this issue if required. It stated that biopsy was included in the clinical trial as a histological endpoint, and was not intended to be a requirement to establish stable disease. The clinical experts said they may do a biopsy as 1 of several clinical parameters to assess whether to stop treatment, but would not expect it to be required in all cases. The committee decided that biopsies may sometimes be used but would not be a requirement, so it may be reasonable to exclude the costs of biopsies (but a scenario including biopsy costs for some people before they temporarily stop treatment may be informative). It would like to

see further evidence exploring pegcetacoplan administration costs in the model, including a proportion of people who would continue to have pegcetacoplan administered by a healthcare professional. The committee concluded it was appropriate to include costs related to vaccinations, antibiotics and cardiovascular events.

Cost-effectiveness estimates

Acceptable ICER

3.16 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- if people can stop treatment with pegcetacoplan, if so how many, and how many people would stay in the stable-disease state without progression for a period of time (see section 3.9)
- how kidney reallocation costs and benefits are captured (see section 3.10)
- utility values used for CKD stages 1 to 5 (see section 3.14).

Because of these uncertainties, the committee could not determine a plausible ICER. But it acknowledged there is an unmet need for people with C3G or IC-MPGN (see section 3.1 and section 3.2) and the conditions are rare, so generating high-quality clinical trial evidence may be challenging. It noted there are some benefits associated with pegcetacoplan that have not been captured in the model (see section 3.19). The committee weighed up the uncertainty in the evidence, the

rarity of the condition, its potential impact on health inequalities (see section 3.18) and the uncaptured benefits. It concluded that, based on the current evidence submitted, an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

The committee's preferred assumptions

3.17 Both the company's and the EAG's base-case ICERs were above the range that NICE considers an acceptable use of NHS resources. The exact cost-effectiveness estimates cannot be reported here because of confidential discounts. The committee's preferred assumptions were that:

- standard care was the relevant comparator (see section 3.3)
- no treatment-effect waning was reasonable (see section 3.6)
- stable disease should be modelled by assuming 20% of people with UPCR less than 1 and with CKD stage 1 would stop treatment, but more analysis is needed on how long this temporary stop of treatment would last (see section 3.9)
- kidney reallocation is a non-reference case analysis and should not be included in the model or cost-effectiveness results, but would be considered as an uncaptured benefit (see section 3.10 and section 3.19)
- both the pegcetacoplan and standard-care arms of the model should be informed by 26-week follow-up data from VALIANT (see section 3.11)
- separate UPCR and eGFR regressions were appropriate (see section 3.12)
- the same transition probabilities should be applied before and after kidney transplantation (see section 3.13)
- pooled utility values from VALIANT for CKD stages 1 and 2 are appropriate. But the EAG's value for CKD stage 3, informed by previous NICE technology appraisals, should be used. CKD stage 4 utility should be the midpoint between the CKD stage 3 and stage 5 values (see section 3.14)

- costs relating to pegcetacoplan administration, vaccination, antibiotics and cardiovascular events should be included (see section 3.15).

Other factors

Equality

3.18 C3G and IC-MPGN are rare and the understanding of the condition varies across renal centre specialists. The committee understood that:

- the conditions are usually diagnosed in young people
- the burden of the condition may disproportionately affect people from some ethnic minority groups or people from lower socioeconomic backgrounds.

As the condition progresses, a kidney transplant may be needed. People from Black and Asian ethnic groups and those who have difficulty finding a match, may have longer waiting times for kidney transplants. The committee noted that pegcetacoplan has the potential to delay the need for a kidney transplant. The committee also noted that these conditions may impact people from a lower socioeconomic background disproportionately, because there is a need for specialist diagnosis, treatment and repeated clinical visits. The committee noted that pegcetacoplan can be administered at home, which may mitigate some access inequalities. The committee also noted that it could only evaluate pegcetacoplan in people over 12 years because those under 12 years were not included in the expected marketing authorisation. The company advised that a trial is planned for children aged 2 to 12 years. The committee concluded that people under 12 years are beyond the remit of the current evaluation, but the other equality issues should be taken into consideration when determining an acceptable ICER.

Uncaptured benefits

3.19 The committee considered whether there were any uncaptured benefits of pegcetacoplan. It noted that C3G and IC-MPGN are often diagnosed in children and young people, and can disrupt education and have a lifetime impact on someone's career and productivity. The committee also acknowledged the additional caregiver burden of looking after a young child with these conditions. The additional time and support needed to take the child to hospital for dialysis and other treatments can have a significant impact on carers' quality of life, making it difficult for carers to maintain relationships and careers. The committee also noted it is important to consider the benefits of pegcetacoplan in reducing the need for kidney transplants, allowing kidneys to go another patients on the NHS waiting list (see section 3.10). The committee concluded that these issues had been reflected in its acceptable ICER.

Conclusion

Recommendation

3.20 Because of the uncertainties in the model, the committee was not able to determine the most plausible ICER. Based on the analysis presented, and taking into account the committee's preferred assumptions, it concluded that the likely cost-effectiveness estimate is above what NICE considers a cost-effective use of NHS resources. So, pegcetacoplan should not be used.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

Lauren Elston and Cara Gibbons

Technical leads

Alan Moore

Technical adviser

Thomas Feist

Project manager

Christian Griffiths

Principal technical adviser

ISBN: [to be added at publication]