NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Iptacopan for treating complement 3 glomerulopathy

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using iptacopan 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: August 2025

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using iptacopan in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 25 September 2025
- Second evaluation committee meeting: TBC
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Iptacopan should not be used to treat complement 3 glomerulopathy in adults, either:

- with a renin-angiotensin system (RAS) inhibitor, or
- alone if a RAS inhibitor is not tolerated or contraindicated.

1.2 This recommendation is not intended to affect treatment with iptacopan 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.

What this means in practice

Iptacopan 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 iptacopan is value for money in this population.

Why the committee made these recommendations

There are no licensed treatments for complement 3 glomerulopathy. Usual treatment aims to control the symptoms. Iptacopan aims to treat the condition.

Clinical trial evidence suggests that, compared with placebo, iptacopan reduces the amount of protein in the urine and slows the decline of kidney function. But this is uncertain because the trials were short and included only a small number of people.

There are significant uncertainties in the economic model, including:

- which evidence should be used

- the assumptions used
- whether the model captures all of iptacopan's potential benefits.

Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimate for iptacopan. Also, all of the cost-effectiveness estimates, from both the company and the external assessment group, are substantially above the range that NICE considers an acceptable use of NHS resources. So, iptacopan should not be used.

2 Information about iptacopan

Marketing authorisation indication

2.1 Iptacopan (Fabhalta, Novartis) is indicated for 'the treatment of adult patients with complement 3 glomerulopathy (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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for iptacopan.

Price

2.3 The list price of iptacopan 200 mg is £26,500.00 for a 56-capsule pack (excluding VAT; BNF online accessed August 2025). The company has a commercial arrangement, which would have applied if iptacopan had been recommended.

Carbon Reduction Plan

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

3 Committee discussion

The evaluation committee considered evidence submitted by Novartis, 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 condition

3.1 Complement 3 glomerulopathy (C3G) is a rare, chronic and progressive kidney condition for which there is no cure. It is an acquired or genetic autoimmune condition, and a type of glomerulonephritis. In C3G, there are issues with the regulation of the complement part of the immune system. This results in the build-up of the C3 protein and inflammation in the kidneys. Common symptoms include high levels of protein in the urine (proteinuria), blood in the urine (haematuria), reduced amounts of urine and swelling in many areas of the body. Diagnosis of C3G is confirmed in specialist renal centres using kidney biopsy. This condition disproportionately affects young people (aged 12 to 17 years). The median age of diagnosis is 22 years, and 44% of people diagnosed are under 18 years. Kidney problems associated with C3G tend to worsen over time and about half of the people affected develop kidney failure within 10 years of their diagnosis. People with kidney failure usually need dialysis or kidney transplantation to stay alive. There are long waits for kidney transplants, and C3G recurrence (kidney dysfunction in the transplanted kidney) is common.

The patient expert conveyed how debilitating C3G can be, especially at the more progressed stages. They said the condition is physically and mentally taxing, it disrupts education and employment, and can negatively impacts relationships. Also, there is little hope for people with the condition because of the lack of treatments that combat the underlying condition. The clinical experts agreed that the prognosis for people with C3G is generally poor. They said that the complement system and the pathophysiology of C3G is well understood. The committee acknowledged

the substantial physical, psychological and social burden of C3G on people and their quality of life. It concluded that there is an unmet need for effective treatments in this rare condition. It noted that, although some people are diagnosed with C3G under 18 years, the market authorisation is limited to adults. So, the committee was disappointed that this evaluation could only evaluate iptacopan for adults.

Clinical management

3.2 There are no disease-modifying treatments for C3G. People usually have treatment to reduce proteinuria, manage hypertension and reduce inflammation. This includes angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor antagonists (ARBs), and immunosuppressants, including corticosteroids. There is no defined clinical pathway and there are no NICE-recommended treatments for C3G. Instead, 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 C3G. 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 clinical experts highlighted the unmet need for a treatment that targets C3G and mitigates the progression of chronic kidney disease (CKD). They said that current treatments only deal with symptoms and that eculizumab is rarely used in clinical practice. The committee acknowledged that existing treatments do not slow the progression of CKD. It concluded that there is a significant unmet need for an effective treatment that could delay CKD progression and kidney replacement therapy (KRT). It also understood that the treatment pathway may need formalising if a new treatment for C3G were to be recommended.

Comparators

3.3 The comparators in the NICE final scope included established clinical management without iptacopan and, for people who had had a kidney transplant and have highly aggressive C3G recurrence, eculizumab. Established clinical management included ACE inhibitors, ARBs, corticosteroids, MMF and sodium–glucose cotransporter-2 (SGLT2) inhibitors. The company submission included a weighted average of all these treatments to represent standard care based on market share data. For people with C3G, the company compared iptacopan plus standard care with standard care alone. But it did not include a comparison of eculizumab with iptacopan for people with a highly aggressive C3G recurrence after a kidney transplant. The company argued that eculizumab was not a relevant comparator (see section 3.4). The committee concluded that the weighted average standard-care approach represented NHS clinical practice and that eculizumab was not an appropriate comparator for post-transplant C3G recurrence.

Relevance of eculizumab as a comparator

3.4 Eculizumab is a monoclonal antibody that prevents the activation of the C5 protein in the complement system and is used to treat some blood disorders. It is routinely commissioned off-label by NHS England (see NHS England's clinical commissioning policy for eculizumab for treating recurrence of C3G after a kidney transplant [PDF only]) for treating highly aggressive C3G recurrence after kidney transplantation. Also, the KDIGO 2021 guideline states that eculizumab should be considered if treatment with MMF plus corticosteroids fails. The company argued that comparing iptacopan with eculizumab would be inappropriate. Based on UK healthcare professional advice, it said that eculizumab is rarely used in the NHS for post-transplant C3G recurrence. It cited that 1 person a year since 2017 has had treatment with eculizumab. It also explained that there is limited data for a comparison of iptacopan with eculizumab, and that any post-transplant iptacopan use would be started before eculizumab

could be offered. This is because of the highly aggressive recurrent disease eligibility requirement for eculizumab. The company identified 3 eculizumab trials. But it deemed them insufficient for supporting an indirect comparison because:

- they lacked common outcomes like eGFR
- they had small sample sizes
- the inclusion criteria differed from the NHS England clinical commissioning policy.

The EAG noted that some relevant outcomes like proteinuria were available, but that the trial population differences would make a meaningful indirect comparison challenging. The company argued that the main reason eculizumab was not a relevant comparator was because it would be offered later in the treatment pathway than iptacopan. The clinical commissioning policy for eculizumab requires highly aggressive C3G, which is defined as a greater than 20% decline in eGFR within the previous 3 months. But any iptacopan use after a kidney transplant would be started at the first signs of C3G recurrence, which is before a relative drop in eGFR could be seen. The clinical experts agreed that iptacopan would be used in the post-transplant subgroup at the first signs of recurrent C3G, such as proteinuria. This differs from the greater than 20% eGFR decline and the crescentic, inflammatory disease that would prompt eculizumab use and that typically takes longer to present. Also, they said that the mechanism of iptacopan acts on the C3 protein, but also switches off the C5 protein. They anticipated that healthcare professionals would have no need to offer eculizumab if iptacopan was a treatment option.

The EAG said that, based on eculizumab being used later in the treatment pathway, there was no need for comparative evidence against iptacopan. But it still had concerns about the limited evidence

for iptacopan use in the post-transplant C3G recurrent subgroup (see section 3.6). The committee concluded that the specific requirements for eculizumab use would preclude its relevance as a comparator for iptacopan in the post-transplant subgroup. So, the company's comparison of iptacopan plus standard care with standard care alone was the only appropriate comparison for this evaluation.

Clinical effectiveness

Data sources

3.5 The key clinical evidence came from the phase 3, randomised controlled APPEAR-C3G (n=71) trial in adults with native kidney C3G. It was supported by evidence from the phase 2, single-arm trial in people with native kidney C3G or post-transplant recurrent C3G (n=27) and an open-label extension study of both trials (n=92). APPEAR-C3G was a randomised, double-blind, parallel group trial in 18 countries (including 3 UK centres). It compared the efficacy and safety of 200 mg iptacopan taken twice daily with placebo over 12 months. The double-blind period was only the first 6 months. After this, participants in both the iptacopan and placebo arms had 200 mg of iptacopan twice daily for a further 6 months, when the trial concluded. The primary outcome was change in proteinuria. Other clinical outcomes included the change from baseline in eGFR, and safety outcomes. The phase 2 trial included native (n=16) and transplant (n=11) kidney cohorts. Participants had 200 mg iptacopan twice daily for up to 21 weeks after a dose escalation phase. Sixty-six people from APPEAR-C3G and 26 people from the phase 2 trial entered the open-label extension study. This study captured longer-term safety and tolerability outcomes.

The key outcomes from the 6-month double-blind period of APPEAR-C3G were change from baseline in proteinuria and eGFR. Iptacopan showed an average 35.1% (95% confidence interval [CI] 13.8% to 51.1%) reduction in 24-hour urine protein-to-creatinine ratio (UPCR) at 6 months

compared with placebo (p<0.01). The change from baseline in eGFR at 6 months was 1.30 ml/min/1.73 m^2 (95% CI -2.14 to 4.73) in the iptacopan arm and -0.86 ml/min/1.73 m^2 (95% CI -4.36 to 2.64) in the placebo arm. This amounted to an adjusted mean difference of 2.16 ml/min/1.73 m^2 (95% CI -2.75 to 7.06) for iptacopan compared with placebo (p=0.32).

In the open-label period of APPEAR-C3G, people in the iptacopan arm had an average reduction from baseline in 24-hour UPCR at 12 months of 40% (95% CI 20% to 55%). People in the placebo arm who had iptacopan in the open-label period had an average 24-hour UPCR reduction from baseline at 12 months of 27% (95% CI 8% to 42%). The change from baseline eGFR at 12 months was 0.44 ml/min/1.73 m^2 (95% CI -3.76 to 4.64) in the iptacopan-to-iptacopan group. This was a numerical drop from 6 months. In the placebo-to-iptacopan group, the change from baseline eGFR at 12 months was 1.15 ml/min/1.73 m^2 (95% CI -3.22 to 5.53).

An exploratory endpoint of APPEAR-C3G including the open-label extension study was a change in eGFR slope analysis (see section 3.12). The mean pre-iptacopan eGFR slope was -7.22 ml/min/1.73 m^2/year (95% CI -10.10 to 4.35). The iptacopan eGFR slop was estimated as -0.29 ml/min/1.73 m^2/year (95% CI -3.88 to 3.31). This amounted to a change in annual eGFR slope of 6.94 ml/min/1.73 m^2 (95% CI 3.48 to 10.39; p=0.0001) compared with pre-iptacopan treatment.

The committee noted that the trials showed that iptacopan provided modest improvements in some outcomes compared with placebo in the short term. It noted that longer-term trial outcomes were not available at this point. It acknowledged that the rarity of the condition can make evidence generation challenging. The committee concluded that the results from the trials were appropriate for decision making, but short durations and small sample sizes meant that the results were uncertain.

Generalisability to post-transplant C3G recurrence

3.6 After a kidney transplant, C3G can affect the transplanted kidney (C3G recurrence). The NICE scope included people who have and have not had a kidney transplant as possible subgroups to be considered. In its submission, the company explained that, given the rarity of the condition and the limited trial enrolments in the post-transplanted C3G population, it is difficult to collate data for this group. The phase 2 single-arm study included data on 11 people with transplanted kidneys. The company presented the trial data but did not include any direct or indirect comparative analyses in the post-transplant subgroup. Consequently, no comparative data was available to inform modelling in post-transplant C3G recurrence. Both the company and EAG acknowledged that data limitations made it challenging to do an adequate treatment comparison in this subgroup. The EAG was concerned about including the post-transplant C3G recurrent subgroup when only analysis in the native kidney group had been presented. When the data allowed, the EAG preferred some indirect comparison of iptacopan and a relevant comparator in the post-transplant group. The company said that opinion from UK healthcare professionals was that the native kidney data would be generalisable to the post-transplant group. This was because C3G impacts native and transplanted kidneys in the same way, and iptacopan has the same mechanism of action in both groups. The company also noted that post-transplant groups were not excluded when only data from a native kidney population was presented in previous NICE technology appraisals guidance in CKD conditions.

The patient expert explained that their enrolment in APPEAR-C3G was on the condition of having a second kidney transplant. They told the committee that they were worried about the risk of C3G recurrence damaging the newly transplanted kidney. But they also said that involvement in a trial with a potentially effective treatment alleviated some of their worries. The clinical experts said that the complement system and

alternative pathway are well understood. They confirmed that iptacopan would act in the same way in both native and transplanted kidneys. They explained they would not expect any difference in the clinical effectiveness of iptacopan in people with native kidneys and transplanted kidneys. Also, they were confident in the generalisability of findings from the native kidney APPEAR-C3G trial to the transplanted kidney C3G recurrent population. The committee noted there was limited evidence to inform analyses in the post-transplant subgroup. But it noted that the clinical experts thought it was clinically and biologically plausible for iptacopan to be at least equally effective in the subgroup of people with a transplanted kidney. The committee concluded that the evidence presented by the company in the cost-effectiveness analyses was generalisable to the post-transplant C3G recurrence subgroup. But it noted that the economic model did not include, or allow for, treatment with iptacopan after a transplant.

Generalisability of trial baseline data

3.7 The company's base case used baseline population data from APPEAR-C3G. The EAG asked if the trial data was generalisable to the NHS. The company said that the trials included UK centres. Also, it described input from UK healthcare professionals confirming that the trial populations reflected the UK C3G population with respect to concomitant medications and proteinuria levels. The company provided population characteristics at the time of C3G diagnosis from the National Registry of Rare Kidney Diseases (RaDaR), with some differences from the population in APPEAR-C3G. The trial population was, on average, younger with higher mean eGFR and a higher proportion of people with CKD stages 1 and 2 compared with the population in RaDaR C3G data. The EAG did not think that the involvement of UK centres in trials was sufficient for showing generalisability. It preferred to use the RaDaR C3G baseline characteristics in its base case. The committee noted the differences in baseline characteristics between the APPEAR-C3G and

RaDaR C3G data. It noted that the C3G portion of RaDaR provided UK real-world data for people with C3G. It concluded that the RaDaR C3G baseline characteristics should be used in the model.

Economic model

Company's modelling approach

3.8 Based on previous CKD NICE technology appraisals guidance, the company chose a Markov model approach that used 9 health states to represent the progression of C3G through CKD stages and KRT. Initially, people entered the model in CKD stages 1 to 4. They could progress to death, higher CKD stages or KRT. Data from APPEAR-C3G informed the baseline characteristics, some utilities, adverse events and eGFR decline, which defined CKD-stage health-state occupation. Unlike other CKD NICE technology appraisals guidance, the company used eGFR slope to model transitions and not observed eGFR. This was because of trial limitations (see section 3.5). The model cycles were 3 months long and a lifetime horizon of 72.1 years was used. The EAG highlighted that, because of the short trial length, the quality-adjusted life years (QALYs) and costs in the model were disproportionality accrued in the observed and extrapolated periods for iptacopan plus standard care and standard care alone. As a simplifying assumption, the company's model did not allow 'improvements' in CKD stage, so people could not move from CKD 2 back to CKD 1. When people reached an eGFR of 7.6 ml/min/1.73 m^2 or less, they were moved proportionally into KRT states of haemodialysis, peritoneal dialysis or kidney transplant. The model did not allow iptacopan use after a transplant. While the EAG noted data limitations persisted, it considered the company's modelling approach to be reasonable. The committee concluded that data availability was a limitation. But it acknowledged that the rarity of the condition presents certain data collection challenges. It concluded that the model structure was acceptable for decision making.

Data used for eGFR slopes to model transitions

3.9 Previous CKD NICE technology appraisals have used observed eGFR data to model state transition probabilities. The company said that limitations of APPEAR-C3G, including the small sample size and few transitions to higher CKD stages, prevented modelling of transition probabilities from the observed data. So, the company modelled transitions through CKD stages using eGFR slopes (the rate of eGFR decline, defined as the average change in eGFR in a 1-year period). The company generated multiple slopes based on different data sets. A healthcare professional advisory board advised the company that eGFR slopes based on the double-blind, 6-month period of APPEAR-C3G were inappropriate. This was because they predicted an average time to kidney failure of 25.7 years. Those healthcare professionals expected kidney failure to occur at around 10 years on average while on standard care (based on RaDaR C3G data). The company's base case used all APPEAR-C3G data for people before they started treatment with iptacopan (pre-iptacopan, n=74, 2.5 years follow up) to represent the standard-care arm eGFR slope. Then it took data for all people taking iptacopan (on-iptacopan, n=74, 2 years of follow up) to represent the iptacopan plus standard-care arm eGFR slope. The company argued that this was the best approach. This was because it predicted a time to kidney failure on standard care of 10 to 11 years, but it also included scenario analyses using slopes from other data sources.

The EAG was concerned that the company's base-case approach was a 'before and after' observational comparison. So, it lost the randomisation from the double-blind period of the trial and may have introduced bias. The EAG's preferred approach used RaDaR data from the C3G population to generate the standard-care arm eGFR slope. Then the EAG applied the observed iptacopan treatment effect from the randomised, double-blind, 6-month period of APPEAR-C3G to the RaDaR C3G standard-care slope to generate the iptacopan arm eGFR slope. It

explained that this approach preserved randomisation for the estimated treatment effect. Also, it used the standard-care eGFR slope based on real-world RaDaR C3G data. The company said that the EAG's approach of using RaDaR C3G data for the standard-care arm eGFR slope predicted an average time to kidney failure of 14 years. The committee noted it would prefer to use the treatment effect from a randomised comparison than an observational one. It concluded that it would prefer to use:

- the specific C3G population that reflected the population eligible for iptacopan from RaDaR as the standard-care baseline eGFR slope
- the iptacopan treatment effect from the randomised period of APPEAR-C3G applied to the standard-care eGFR slope.

Constant eGFR decline

3.10 The company's model assumed that eGFR declines at a constant rate at all times and independently of CKD stage. The EAG was concerned that this was an unrealistic assumption because eGFR could decline at a different rate as the KRT stage approaches. The company said that the sample size of the iptacopan trials were too small to estimate a CKD-stage-dependent eGFR decline rate. The company sought clinical advice. This confirmed that, despite eGFR fluctuations, the general trend of eGFR decline was linear and they would not expect any speeding up of decline closer to KRT. The EAG had suggested approaches that would model CKD-stage or time-dependent eGFR decline rates from the C3G trials, but the company did not provide these. This remained a source of uncertainty for the EAG, and it was unclear how this could affect the long-term modelling of costs and benefits. The clinical experts said that, in clinical practice, nephrologists may use a person's eGFR from the previous year to predict how eGFR may decline in the future. But nephrologists are generally focused on eGFR falling below 10 ml/min/1.73 m^2 as an indication of need for transplant, and not on eGFR decline itself. Both clinical experts agreed that the linear decline of eGFR independent of

CKD stage is used in clinical practice and was a reasonable approach. The committee acknowledged it was not possible to estimate eGFR decline dependent on CKD stage from the data available. The committee noted the rarity of the condition and the difficulty in generating trial evidence. It noted that there may still be some uncertainty in the assumption that eGFR declines linearly. But it concluded that, although a simplification, a linear rate of decline was appropriate for modelling. It noted that it would like to see exploration of eGFR decline varying in the later stages of CKD, supported by evidence when available, even if this is from other kidney diseases.

Constant treatment discontinuation

3.11 The company modelled iptacopan treatment discontinuation for people who have not reached kidney failure using an annual rate of 6.3% based on the iptacopan C3G broad safety set (n=101). This was applied as 1.57% in all 3-month model cycles before KRT. The EAG questioned whether a constant treatment discontinuation rate while on iptacopan before kidney failure was appropriate. It was concerned that, in the absence of long-term data, a constant discontinuation rate for iptacopan over time seemed implausible. At the clarification stage, the company provided time-to-discontinuation analyses for APPEAR-C3G and for the pooled iptacopan trials. It did scenario analyses using the best-fitting exponential and log-normal curves, and found that the incremental cost-effectiveness ratios (ICERs) were affected modestly. Although the EAG welcomed the additional analyses, it was concerned that full details of the healthcare professional input and curve selection did not follow the NICE Decision Support Unit technical support document 14 on survival analysis. Consequently, the EAG could not fully scrutinise the company's approach. Also, the EAG was concerned that the modest impact from the company's additional treatment discontinuation analyses may increase if treatment waning was applied (see section 3.12).

The clinical experts were unsure whether a constant treatment discontinuation rate should apply indefinitely. They thought that iptacopan use could alter the natural history of C3G, and no evidence for understanding how iptacopan will be used or stopped in the long term exists. The committee asked the clinical experts whether people would take iptacopan indefinitely in the absence of an adverse event. The clinical experts explained that they would likely choose to treat eligible populations with iptacopan up front. But they added that it was unclear how well people's condition would respond to iptacopan treatment over time. They anticipated that iptacopan use could be reviewed and stopped if it showed no benefit. The committee noted that the model had no functionality to reflect this. It asked whether more adverse events would be expected in the first couple of years or in the long term. The company replied that the safety profile of iptacopan in C3G is consistent with longer-term real-world evidence on adverse events related to iptacopan use from other indications. The committee noted that there was uncertainty about long-term treatment discontinuation. It concluded that, while there remained unresolvable uncertainties at this time, the company's constant treatment discontinuation was an acceptable approach.

Iptacopan treatment waning

3.12 Based on the sustained treatment effect across APPEAR-C3G and the extension studies, the company modelled a constant treatment effect for iptacopan. This implied that there would be no waning of the treatment effect over time. But the EAG thought that this assumption was not sufficiently justified over a 72.1-year lifetime horizon. The clinical experts noted the difference between treatment waning and lack of effect. They both agreed that, while taking iptacopan, the C3 activity block would persist and there was no indication that there would be any waning of the relative iptacopan treatment effect. Clinical expert opinion to the company and the EAG agreed that the on-target effect of iptacopan on complement

inhibition remains the same over time. Although the EAG thought further waning scenario analyses could be done, the company said that the limited CKD-stage changes in the trial rendered that unfeasible. The committee concluded that, based on iptacopan's mechanism of action, a constant treatment effect is a reasonable assumption. It noted uncertainty related to possible waning along with limited trial data, unclear long-term treatment discontinuation and extrapolation over a lifetime. When data allows, the committee would welcome a treatment effect waning scenario with formal comparison of treatment arm effects.

Utility values

3.13 The company used observed EQ-5D-5L data from APPEAR-C3G mapped to the EQ-5D-3L to inform utility values for CKD stages 1 to 4. Utilities for CKD stage 5, haemodialysis, peritoneal dialysis and post-transplant were not available from APPEAR-C3G. So, the company used utility values from Jesky et al. (2016) for CKD stage 5 and Lee et. al (2005) for haemodialysis, peritoneal dialysis and post-transplant. It applied age adjustments to account for differences between the C3G and general CKD populations. The EAG used the company's utility values in its base case. But it explained that it would expect the post-transplant utility value to be higher than the adjusted modelled value of 0.76 based on Lee et.al (2005). The EAG provided an exploratory scenario analysis using an adjusted utility value of 0.86 for the post-transplant health state, based on Liem et. al (2008). The EAG highlighted that increasing the post-transplant utility value increased the ICER. The patient expert explained that, in their experience, a transplant improved their quality of life substantially compared with CKD stage 5 and dialysis, so they would expect the post-transplant health state to have a higher utility value than CKD stage 5. The committee questioned what health states the post-transplant utility value represented in the model. The EAG explained that the utility value for the post-transplant health state represented the average quality of life for someone from the point of having a transplant

until transplant failure and needing another transplant. It clarified that there was no explicit modelling of the individual CKD stages in the post-transplant state. The committee noted that there may be additional negative impacts on quality of life after a transplant because of worries about rejection or having to take additional medicines. The committee concluded that the company's and EAG's base-case approach for CKD stage 5, haemodialysis, peritoneal dialysis and post-transplant utilities was appropriate for decision making. But it requested exploratory analyses using a weighted average of the CKD stages 1 to 5 utility values to inform the post-transplant utility value.

Cost-effectiveness estimates

Acceptable ICER

3.14 NICE's manual on health technology evaluations 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 that:

- clinical-effectiveness evidence from the short APPEAR-C3G trial was extrapolated over a long time horizon in the economic model (see section 3.8)
- there was limited data informing the eGFR slopes (see section 3.9)
- some inputs in the economic model were only informed by clinical expert input (see section 3.11)
- a constant treatment discontinuation rate was assumed without strong evidence to support this (see section 3.11)
- a constant treatment effect for iptacopan was assumed without strong evidence to support this (see section 3.12)

- the utility values for CKD stage 5 and KRT were sourced from the literature rather than trial data (see section 3.13).

The committee acknowledged that there is an unmet need for people with C3G and that C3G is rare, so generating high-quality clinical trial evidence may be challenging. It also noted that there may be some benefits associated with iptacopan that may not have been captured in the model (see section 3.17). The committee weighed up the uncertainty in the evidence, the rarity of C3G, its potential impact on health inequalities and the uncaptured benefits. It concluded that 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

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

- that eculizumab is not a relevant comparator (see section 3.4)
- that evidence for native kidneys is generalisable to transplanted kidneys (see section 3.6)
- using baseline characteristics from RaDaR C3G data (see section 3.7)
- using eGFR slopes for standard care generated using RaDaR data specific to the C3G population eligible for iptacopan (see section 3.9)
- using eGFR slopes for iptacopan generated by applying the iptacopan treatment effect from the randomised period of APPEAR-C3G to standard-care eGFR slopes (see section 3.9)
- using a linear rate of eGFR decline (see section 3.10)

- applying a constant rate of treatment discontinuation from pooled iptacopan trials (see section 3.11)
- using a constant treatment effect for iptacopan (see section 3.12)
- basing CKD stage 5 utilities on Jesky et al. (2016; see section 3.13)
- basing haemodialysis, peritoneal dialysis and post-transplant utilities on Lee et al. (2005; see section 3.13)
- modelling of all grade 3 and higher adverse events from the controlled safety set regardless of relationship to iptacopan.

The committee also requested the following further exploratory analyses:

- an eGFR decline that varies in the later stages of CKD, if evidence is available to inform this
- including iptacopan use after a transplant in the model
- using a weighted average of CKD stages 1 to 5 utility values to inform the post-transplant utility value.

Other factors

Equality issues

3.16 C3G is rare and the understanding of the condition varies across renal centre specialists. The committee heard that:

- C3G is usually diagnosed in earlier adulthood
- the burden of the condition may disproportionately affect:
  - certain ethnic minority groups
  - people from some socioeconomic backgrounds.

As the condition progresses, a kidney transplant may be needed. People from Black and Asian ethnic backgrounds may have longer waiting times for kidney transplants than people from White ethnic backgrounds. The committee noted that iptacopan has the potential

to delay the need for a kidney transplant. The committee was disappointed that, at this time, it could only evaluate iptacopan for adults. It concluded that iptacopan could delay the need for KRT and may reduce health inequalities associated with kidney transplant waiting times.

Uncaptured benefits

3.17 The committee considered whether there were any uncaptured benefits of iptacopan. It noted that the economic model did not include iptacopan use after a transplant even though it could be used in this way according to its marketing authorisation. The committee recalled the clinical experts explaining that iptacopan might be more clinically effective after a transplant. This is because treatment with iptacopan could be started earlier, before damage to the transplanted kidney (see section 3.6). It also recalled that iptacopan use may delay progression to later-stage CKD and KRT, benefitting the broader CKD population who need KRT (see section 3.16). These additional considerations were reflected in the committee's acceptable ICER.

Conclusion

Recommendation

3.18 The committee took into account its preferred assumptions and acceptable ICER, and the company’s and EAG’s base cases. It recalled that all of the ICERs were substantially above the range that NICE considers an acceptable use of NHS resources. It noted that the company had not submitted a managed access proposal, and there were no plausibly cost-effective ICERs. It concluded that iptacopan should not be used to treat C3G in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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

Megan John
Chair, technology appraisal committee D

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.

Sammy Shaw
Technical lead

Nigel Gumbleton
Technical adviser

Kate Moore
Project manager

Christian Griffiths

Principal technical adviser

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