NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Sparsentan for treating primary IgA nephropathy

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

Note that this document is not NICE's final guidance on sparsentan. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using sparsentan in the NHS in England.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 March 2025
- Second evaluation committee meeting: 9 April 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Sparsentan should not be used to treat primary immunoglobulin A nephropathy (IgAN) in adults with a:

- urine protein excretion of 1.0 g/day or more, or
- urine protein-to-creatinine ratio of 0.75 g/g or more.

1.2 This recommendation is not intended to affect treatment with sparsentan 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

Sparsentan is not required to be funded in the NHS in England to treat primary IgAN in adults with a urine protein excretion of 1.0 g/day or more, or a urine protein-to-creatinine ratio of 0.75 g/g or more. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that sparsentan offers value for money.

Why the committee made these recommendations

Standard care for primary IgAN includes angiotensin-converting enzyme inhibitors or angiotensin receptor blockers such as irbesartan. Sodium-glucose cotransporter-2 inhibitors are also often used.

Clinical trial evidence shows that sparsentan reduces the urine protein-to-creatinine ratio (the amount of protein in the urine) more than irbesartan. Evidence also suggests that sparsentan is better at maintaining kidney function than irbesartan, but this is uncertain.

There are uncertainties with some assumptions used in the economic model, including how sparsentan would be used in clinical practice.

Because of the uncertainties in the clinical evidence and economic model it is not possible to determine the most likely cost-effectiveness estimates for sparsentan. So, it should not be used.

2 Information about sparsentan

Marketing authorisation indication

2.1 Sparsentan (Filspari, Vifor) is indicated for 'the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥ 1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for sparsentan (PDF only).

Price

2.3 The list price is £3,401.71 per 30-pack of 200 mg tablets or £3,401.71 per 30-pack of 400 mg tablets (excluding VAT; company submission).

2.4 The company has a commercial arrangement, which would have applied if sparsentan had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Vifor, 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

Details of immunoglobulin A nephropathy

3.1 Immunoglobulin A nephropathy (IgAN) is a progressive chronic kidney disease (CKD) caused by the buildup of IgA antibodies in the kidneys,

leading to inflammation and scarring. This can result in kidney failure (end-stage renal disease, ESRD). In primary IgAN, there is no clear cause, but genetic and environmental factors, such as exposure to toxins, may contribute. The condition is often asymptomatic in early stages and is typically diagnosed through a kidney biopsy. IgAN progression is measured by estimated glomerular filtration rate (eGFR), which assesses how well the kidneys filter waste. CKD stages range from stage 1 (eGFR more than 90 ml/min/1.73 m², normal function) to stage 5 (eGFR less than 15 ml/min/1.73 m², kidney failure). IgAN is the leading cause of kidney failure in people under 40 years and progresses faster than other CKD types. A patient expert explained that people with IgAN often face prolonged delays in accessing specialist care or transplantation, which can result in worsening eGFR levels. Between 45% and 70% of people with IgAN develop kidney failure within 10 to 20 years, often requiring a kidney transplant or lifelong dialysis. But patient experts and clinical experts emphasised that kidney transplantation does not stop IgAN because it can recur in the transplanted kidney. Limited donor availability and increasing pressure on dialysis services further restrict treatment options. The patient experts highlighted that IgAN is not a curable disease but rather a condition that must be managed to delay irreversible kidney damage. Clinical experts stated that proteinuria (high protein levels in urine) is a key risk factor for faster progression, typically measured by the urine protein-to-creatinine ratio (UPCR).

Effect on quality of life and unmet need

3.2 Patient experts highlighted that IgAN has a profound impact on quality of life, particularly for younger adults, affecting their ability to work, travel, and maintain relationships. Many described IgAN as a condition that gradually worsens, leading to an inevitable decline in kidney function, with limited treatment options. People with IgAN often experience substantial mental health challenges, including anxiety and depression, because of the uncertainty surrounding disease progression and the lack of specific treatments to slow or prevent this. Current treatments are associated with

substantial risks and burdens. Corticosteroids, while sometimes used, can cause severe side effects such as mood changes and confusion, with only limited long-term benefits. Dialysis and transplantation are high-risk, invasive procedures that do not offer a cure. Patient experts expressed concern that a kidney transplant, though a potential option, is not a definitive solution and comes with lifelong challenges. They also highlighted that immunosuppressive treatment, which is needed after transplantation, increases the risk of cancer and other serious side effects. There remains an urgent need for disease-modifying treatments that can slow IgAN progression and delay or reduce the need for dialysis and transplantation. Patient experts emphasised that a treatment capable of modifying the disease course would be a significant step forward, offering hope for improved long-term outcomes. The committee concluded that IgAN has a substantial physical and psychological burden on people with IgAN, their families and healthcare services, and that new treatments are needed.

Clinical management

Treatment pathway and positioning

3.3 The patient and clinical experts highlighted that there is no available cure for IgAN, and current pharmacological treatments aim to delay disease progression by reducing proteinuria and controlling blood pressure. They explained that the treatment pathway is closely aligned with the Kidney Disease Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. This recommends maximally tolerated renin-angiotensin system inhibitors (RASi), such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), as standard care. Given its ARB activity, clinical experts noted that sparsentan effectively replaces traditional RASi therapy and offers additional proteinuria-lowering effects.

Lifestyle modifications and dietary interventions also form part of standard care. Statins are also used to manage cardiovascular risk and sodium-

glucose cotransporter-2 (SGLT2) inhibitors are used for their kidney-protective and cardiovascular benefits. The clinical experts said that SGLT2 inhibitors are not comparators, because they can be used alongside both RASi and sparsentan, and are increasingly part of standard care for IgAN.They also highlighted early evidence from the SPARTACUS trial and other ongoing studies showing that SGLT2 inhibitors work synergistically with RASi therapy to reduce proteinuria. Initial data suggests that combining a dual endothelin and angiotensin receptor antagonist (such as sparsentan) with an SGLT2 inhibitor results in incremental reductions in proteinuria, further supporting their complementary use. Clinical experts said that targeted-release budesonide (TR-budesonide) is not a relevant comparator. This is because TR-budesonide is an add-on treatment when there is a risk of rapid disease progression, as recommended in NICE's technology appraisal guidance on TR-budesonide for treating primary IgAN. The clinical experts noted that sparsentan and TR-budesonide have distinct mechanisms of action and are likely to be used together rather than as alternatives. They also stated that they do not expect a ceiling effect on efficacy when combining treatments with different modes of action. But the committee noted that these treatments have not been widely used together in clinical practice. Clinical experts noted that the only way to effectively prevent ESRD in IgAN is through combination therapy that targets multiple pathways involved in disease progression. They highlighted that time to ESRD is strongly influenced by proteinuria levels before and after starting treatment, reinforcing the importance of multifaceted early intervention. The committee concluded that sparsentan would replace RASi therapy, and be used in addition to current standard care, which includes SGLT2 inhibitors and TR-budesonide in people with a UPCR of 1.5 g/g or more. So, SGLT2 inhibitors and TR-budesonide are not comparators.

RASi as a comparator

3.4 The company submission included irbesartan, an ARB, as the only comparator for sparsentan, representing standard RASi therapy. Having concluded that RASi therapy is an appropriate comparator for sparsentan (see section 3.3), the committee considered whether irbesartan is representative of RASi therapy used within the NHS. Clinical experts confirmed that irbesartan is commonly used within the NHS and that sparsentan shares similar ARB activity, so irbesartan would be replaced by sparsentan if it were available. The committee concluded that irbesartan is an appropriate comparator.

Clinical effectiveness

Key clinical trial: PROTECT

3.5 The clinical evidence for sparsentan was from PROTECT. This randomised, double-blind, phase 3 clinical trial compared sparsentan (n=202) with irbesartan (n=202) in adults with biopsy-confirmed primary IgAN and persistent proteinuria despite at least 12 weeks of stable, maximum RASi therapy. The primary outcome was the percentage change in UPCR from baseline to week 36. Sparsentan statistically significantly reduced proteinuria measured using UPCR compared with irbesartan at both week 36 and week 110. The geometric least squares (LS) mean percent change from baseline was -49.8% with sparsentan compared with -15.1% with irbesartan at week 36 (geometric LS mean ratio 0.59; 95% confidence interval [CI] 0.51 to 0.69). By week 110, reductions were -42.8% with sparsentan compared with -4.4% with irbesartan (geometric LS mean ratio 0.60; 95% CI 0.50 to 0.72).

Key secondary outcomes included the chronic eGFR slope and total eGFR slope. These show the rate of kidney function decline over time. The chronic slope excludes the acute effects of initial treatment. The annualised decline in eGFR from week 6 to week 110 (chronic slope) was -2.7 ml/min/1.73 m² per year with sparsentan compared with -3.8 ml/min/1.73 m² per year with irbesartan. This corresponded to a difference of 1.1 ml/min/1.73 m² per year. While this chronic slope

reduction was statistically significant (p=0.037), the total eGFR slope reduction from day 1 to week 110 did not reach statistical significance (difference per year 1.0; 95% CI -0.03 to 1.94, p=0.058). The committee thought that the total slope results were inconclusive, limiting the ability to project long-term benefits for endpoints such as ESRD, dialysis and mortality. However, the company and clinical experts emphasised that chronic slope is more relevant for long-term modelling, because the total slope includes an acute treatment effect that occurs only once when starting treatment. The committee were aware that sparsentan currently has a conditional marketing authorisation. The company advised that further data submitted to the Medicines and Healthcare products Regulatory Agency will support a full marketing authorisation. The committee agreed that any further data collected in response to the conditional marketing authorisation, that was not included in the original company submission, may provide more certainty around long-term efficacy results.

Other secondary outcomes included proteinuria remission rates and a composite kidney failure endpoint (40% or more eGFR reduction, ESRD, or death). Complete proteinuria remission occurred in 21% of people in the sparsentan arm compared with 8% in the irbesartan arm at week 36, while partial remission (UPCR below 1.0 g/g) occurred in 70% compared with 44%. Fewer people in the sparsentan arm had kidney failure events (9% compared with 13%), although this difference was not statistically significant (relative risk 0.68; 95% CI 0.37 to 1.24). The safety profile of sparsentan was comparable to irbesartan, with treatment-emergent adverse events leading to discontinuation in 10% of people on sparsentan compared with 9% on irbesartan. The committee concluded that sparsentan provided statistically significant reductions in proteinuria and a similar safety profile to irbesartan. But that there is uncertainty in the long-term benefit of sparsentan because the total eGFR slope was not statistically significant.

Concomitant treatments in PROTECT

3.6 People in PROTECT were randomised to have either sparsentan or irbesartan alongside standard care. Standard care included lipid-lowering medications, antihypertensive medications and SGLT2 inhibitors. Only 4% of people in the sparsentan arm and 6% of people in the irbesartan arm had SGLT2 inhibitors. The committee recalled that SGLT2 inhibitors are increasingly part of standard care for IgAN and thought that this was not reflected in PROTECT. The clinical experts advised that an initial data cut from the SPARTACUS trial, an ongoing single-arm study in which SGLT2 inhibitors are used alongside sparsentan, is available. Although the committee understood that SGLT2 inhibitors would be used as part of standard care as well as sparsentan, it noted that this data was not included in the company submission and that the committee had not seen the available data to determine whether the effect was fully additive. The committee further noted that it had not been presented with any evidence on using sparsentan alongside TR-budesonide (for people with a UPCR 1.5 g/g or more). The clinical experts advised that the use of sparsentan alongside TR-budesonide has not yet been studied in clinical trials. The experts expected the treatment effective to be cumulative. The committee noted that no evidence was currently available. The committee concluded that the concomitant treatments in PROTECT do not fully reflect how sparsentan would be used in the NHS. It requested data from SPARTACUS to assess the impact of using SGLT2 inhibitors alongside sparsentan.

RASi dose titration

3.7 The dose titration of RASi therapy in PROTECT is higher than in other IgAN studies. In PROTECT, 97% of people in the irbesartan arm were titrated to the maximum recommended dosage. NefIgArd Nef-301 (the key clinical trial for TR-budesonide) had less rigorous RASi optimisation in the RASi arm, with only 48% of people having 80% or more of the maximum dose. The company suggested that the higher RASi dosing in PROTECT may have led to a smaller observed treatment effect for sparsentan,

because the comparator arm (irbesartan) showed a greater reduction in UPCR and a slower decline in eGFR compared with other trials. The clinical experts noted that RASi dosing in the NHS is typically suboptimal, suggesting that the irbesartan arm in PROTECT may not be representative of usual clinical practice. The clinical experts stated that sparsentan will require fewer dose adjustments compared with most RASi therapies, which may allow for more rapid treatment optimisation. Because people are not seen frequently, this may mean the benefit of sparsentan seen in PROTECT is underestimated. The EAG noted that the dose optimisation in PROTECT was higher than would be expected in the NHS for both sparsentan and irbesartan. The committee agreed that the trial demonstrated the likely efficacy of sparsentan compared with RASi and should be used to model efficacy. It also noted that the effect of sparsentan compared with RASi in clinical practice could be greater than observed in the trial because RASi dosing in the NHS is typically suboptimal. The committee concluded that the impact of RASi dose titration on the treatment effect of sparsentan remains uncertain, and its generalisability to clinical practice in the NHS is unclear.

Comparison with TR-budesonide

3.8 The company did a matching-adjusted indirect comparison (MAIC) analysis of sparsentan compared with TR-budesonide using data from the PROTECT and NefIgArd Nef-301 trials to assess comparative effectiveness. The MAIC was not done in the indicated subgroup for TR-budesonide (people with a baseline UPCR of 1.5 g/g or more). This was because baseline characteristics for this subgroup were not reported from NefIgArd Nef-301. The committee recalled that TR-budesonide is not a relevant comparator for sparsentan and clinical experts would prefer to use TR-budesonide and sparsentan together. The committee concluded that a comparison with TR-budesonide was not required for decision making.

Economic model

Company's modelling approach

3.9 The company developed a health economic model to assess the cost effectiveness of sparsentan compared with standard care for people with IgAN. The model used a cohort-level state transition approach to simulate disease progression, with health states defined by composite CKD stages and UPCR levels for people without ESRD. Additional health states included pre-renal replacement therapy, dialysis, kidney transplant, and death. The EAG thought that the model structure was reasonable and aligned with previous technology appraisals. The committee concluded that the company's approach was broadly acceptable for decision making.

Starting sparsentan

3.10 The company's model includes people with CKD stages 1 to 4 in the sparsentan treatment arm, assuming that a proportion of the initial cohort enter the model in CKD stage 4 and begin treatment. The summary of product characteristics for sparsentan states that it is not recommended in people with severe kidney disease (CKD stage 4 or 5, defined as eGFR below 30 ml/min/1.73 m^2) because of limited clinical experience. The company justified the inclusion of people with CKD stage 4 because of fluctuations in proteinuria and eGFR levels between screening and baseline visits in PROTECT. Additionally, the company model assumed that people who progress to CKD stage 4 while on sparsentan will continue treatment unless they meet discontinuation criteria related to disease progression or background discontinuation. The EAG restricted the use of sparsentan in its base case to people with CKD stages 1 to 3 to align with the summary of product characteristics. The EAG's clinical advisers reported that they would adhere to the summary of product characteristics by not starting treatment at CKD stage 4 and stopping treatment in people with sustained eGFR values (below 30 ml/min/1.73 m^2) suggesting CKD stage 4 progression. The clinical experts at the committee meeting stated that they would prefer some

flexibility to allow continuation of sparsentan in people with an eGFR below 30 ml/min/1.73 m^2. The committee noted that using sparsentan in people with CKD stage 4 would be off-label and that it could only consider a treatment within its marketing authorisation. So, it concluded that the model should reflect the marketing authorisation and align with the population in the summary of product characteristics, meaning only people with CKD stages 1 to 3 would be eligible for sparsentan.

Stopping rule

3.11 The company's model incorporates a week 36 stopping rule, requiring discontinuation of sparsentan in people with a 'UPCR of 1.76 g/g or more and or a 20% or lower reduction from baseline'. This stopping rule was not part of the PROTECT trial. The company stated that it was included because no treatment effect would be expected if proteinuria (measured using UPCR) remains high at 36 weeks. The EAG supported the concept of a stopping rule but highlighted uncertainty about the definition of 'non-response', particularly whether people with a UPCR below 1.76 g/g but with less than 20% reduction in UPCR from baseline should be classified as responders or non-responders. The company clarified at the committee meeting that, in contrast to the company's submission, the stopping rule applied in its model requires discontinuation of sparsentan in people with a 'UPCR of 1.76 g/g or more and a 20% or lower reduction from baseline'. But, the stopping rule in the model did not apply to people that have UPCR of 1.76 g/g or more and a 20% or lower reduction from baseline. The clinical experts advised that treatment decisions should be based on proteinuria reduction, because proteinuria is a key predictor of long-term kidney function decline and can be easily monitored at every clinic visit. They stated that if a treatment is not showing an effect on proteinuria, it is unlikely to provide meaningful renal protection, and continuing an ineffective treatment would not be justified. However, they also noted that some people with persistent proteinuria may still derive benefits from sparsentan, particularly if there is gradual proteinuria reduction or improvements in blood pressure control. Patient experts expressed

substantial concerns about the stopping rule, noting that it may be difficult for people to understand why their treatment is being withdrawn, particularly if they perceive it as a loss of care rather than an evidence-based decision. They highlighted the psychological impact of stopping treatment, particularly given the limited treatment options for IgAN. The committee acknowledged that stopping treatment based solely on a predefined threshold could create confusion for patients. They also noted that the application of the company's proposed stopping rule in NHS clinical practice would be challenging. Given the uncertainty surrounding the stopping rule, the committee requested analyses with and without the stopping rule for all scenarios, rather than only considering scenarios in which it is applied. The committee concluded that the stopping rule currently proposed by the company may be difficult to implement and that further clarification around how a stopping rule would work in the NHS is needed.

CKD transition probabilities

3.12 In the company's model, transition probabilities between UPCR categories were estimated using data from PROTECT. CKD stage transitions were informed by external data from the UK Registry of Rare Kidney Diseases (RaDaR), a national registry collecting real-world data on rare kidney conditions, rather than observed transitions from PROTECT. The company justified this approach by citing evidence that reductions in proteinuria are associated with slower CKD progression, referencing surrogate validation studies of other IgAN treatments. The clinical expert stated that proteinuria reduction is an established surrogate for kidney outcomes and that there is a well-documented linear relationship between proteinuria reduction and long-term CKD progression, which is independent of treatment mechanism. The clinical expert also stated that this relationship has been validated using prospective and retrospective data and was instrumental in regulatory approvals, which supports the use of proteinuria reduction as a predictor of CKD progression. The committee recalled that PROTECT showed a statistically significant reduction in

proteinuria with sparsentan but did not show a significant impact on total eGFR slope (see section 3.5). The company explained that using eGFR-based CKD transitions based on a 2-year trial setting was difficult because most people's CKD stage moved by only a fraction over this period. The company stated that given the small magnitude of CKD progression within PROTECT, the construction of transition matrices based on this data alone introduces considerable uncertainty. The company further explained that, while the population size in RaDaR was similar to PROTECT, the longer follow-up period meant that more data on transitions between CKD stages was available. The EAG used data from PROTECT in its base case. It was concerned about the company's reliance on RaDaR data rather than exclusively using PROTECT for CKD progression estimates. The EAG also stated that the company had not provided sufficient explanation of how the transition probabilities were estimated from RaDaR. The committee considered the validity of estimating the transition probabilities from RaDaR. The EAG suggested that its model predictions based on PROTECT provide a better representation of the observed proportion of people in each CKD stage at week 108 compared with the company's base-case model using RaDaR. The clinical experts advised that the proportion of people in the ESRD health state at week 108 seemed high, but not implausible. The committee recalled that the clinical trial for TR-budesonide had a shorter duration and fewer participants than PROTECT. In that appraisal, the company supplemented its trial data with real-world evidence from the RaDaR database to inform later-stage transitions. The committee suggested that to make best use of the available data, the model could incorporate elements of both PROTECT and RaDaR data. This would align to the approach used in the TR-budesonide model, using observed CKD transitions from PROTECT when feasible and supplementing with RaDaR data when trial-derived estimates are limited. These analyses should be externally validated to ensure that long-term projections align with clinical expectations. The committee concluded that it preferred for the CKD transition probabilities to be based on data from PROTECT. It

requested a scenario primarily using PROTECT data but supplemented by RaDaR data for the later CKD stage transitions between CKD stage 4 and stage 5 (ESRD).

Costs

Health state costs

3.13 The company's base-case cost model uses health state costs based on CKD stage and UPCR level. It incorporated data from NHS Reference Costs, a CKD costing study by Pollock et al. (2022), and real-world evidence from the TriNetX database, referred to as IQVIA costs. The company generated these health state costs to be specific to people with IgAN. The EAG raised concerns about the validity and transparency of the IQVIA costs. It stated that there were errors in how costs were mapped between urine albumin-to-creatinine ratio and eGFR states, leading to incorrect CKD stage categorisation. It also noted that arbitrary assumptions were used. The EAG used health state costs from Pollock et al. for hospitalisations, outpatient appointments and emergency visits in its base case. It provided a scenario using costs from Pollock et al. over a broader range of cost categories including critical care and ambulance use. It noted that these costs were not specific to people with IgAN but for people with CKD. The clinical experts highlighted key differences between IgAN and the broader CKD population represented in Pollock et al. They stated that IgAN is a kidney-specific disease that presents earlier in life, with fewer comorbidities than other CKD types. They noted that costs may be lower for earlier CKD stages, which aligns more closely with the company's approach than Pollock et al. But they noted that there was no explanation for why costs using the company's approach were higher at later CKD stages when compared with Pollock et al. The company argued that the Pollock et al. study may not accurately reflect the costs associated with IgAN. The company stated that the IQVIA costs align better with those used in NICE's technology appraisal guidance on TR-budesonide for treating primary IgAN than with costs from Pollock et al. The committee noted that the company's assumption that people with

IgAN incur meaningfully different healthcare costs than other people with CKD who have equivalent UPCR and eGFR levels was not supported by direct evidence. The committee thought that while IgAN-specific cost data may be reasonable to consider, the methodological concerns with the IQVIA costs introduced too much uncertainty. It thought that Pollock et al. was a more transparent cost source. It recalled that 2 sets of costs were available from this, those used in the EAG base case and a broader set of costs using all cost categories. The committee wanted to understand whether the higher costs in the broader dataset better captured the additional healthcare costs associated with IgAN. It requested further explanation of the costs and analyses using both the EAG base-case costs and the broader set of costs to explore this further. The committee concluded that health state costs should be based on Pollock et al., and that analyses should use both the costs in the EAG base case and those for all cost categories to provide a more comprehensive assessment.

Other factors

Equality

3.14 The committee noted that IgAN disproportionately affects certain ethnic groups, particularly people of Asian and Black ethnicity. Clinical experts noted that not only is the prevalence of IgAN higher in these populations, but disease progression is often faster, leading to an increased risk of ESRD. The committee recognised that access to renal transplantation is often more challenging for these groups, with longer waiting times for suitable donor matches, which may result in prolonged dependence on dialysis. Race is a protected characteristic under the Equality Act 2010. The committee acknowledged the potential equality considerations related to IgAN but noted that it had not yet seen cost-effectiveness results incorporating all of its preferred assumptions. It requested further analyses to address uncertainties in the evidence and agreed to consider equality issues once it has reviewed these.

Uncaptured benefits

3.15 The committee considered whether there were any uncaptured benefits of sparsentan. The company highlighted that health-related quality of life (HRQoL) in the model was based on CKD stage alone and did not account for the potential impact of proteinuria reduction on wellbeing. Clinical and patient experts noted that proteinuria contributes to physical symptoms such as fatigue and swelling, as well as psychological distress, particularly in younger people concerned about disease progression and the need for future dialysis or transplantation. The committee noted that the model used utility data based on CKD stage, and the available data did not explicitly include proteinuria-related HRQoL benefits in the model but that these might have been captured implicitly. Patient experts highlighted that people with long-term exposure to immunosuppressants, typically after kidney transplant, face cumulative risks of cancer and other adverse effects, reinforcing the need for additional treatment options that can potentially delay progression to ESRD. Clinical and patient experts also highlighted that the demand for renal services is increasingly impacting on availability of dialysis and waiting times for transplants, so a treatment that could preserve kidney function would be valuable. The committee recognised these issues and concluded that there were uncaptured benefits of sparsentan to take into account in its decision making.

Cost-effectiveness estimates

Acceptable ICER

3.16 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year 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:

- PROTECT did not show a statistically significant improvement in total eGFR slope, so there is uncertainty in the longer-term outcomes used in the model (see section 3.5)
- PROTECT did not evaluate sparsentan or irbesartan alongside SGLT2 inhibitors (see section 3.6)
- dose titration in PROTECT was higher and happened more quickly than is expected in the NHS (see section 3.7)
- a stopping rule is applied at week 36 which may be difficult to implement in the NHS (see section 3.11)
- CKD transition probabilities are based on data from RaDaR, rather than from PROTECT (see section 3.12)
- health state costs based on the IQVIA cost analysis are unreliable (see section 3.13).

The committee was unable to identify an acceptable ICER threshold because this would need to account for the resolvable uncertainties in the requested analyses (see section 3.17).

Company and EAG cost-effectiveness estimates

3.17 The exact cost-effectiveness estimates cannot be reported here because there are confidential discounts for sparsentan. Both the company's and EAG's base-case ICERs were above the range that NICE normally considers an acceptable use of NHS resources. However, neither the company's nor the EAG's base-case ICERs included all the committee's preferred assumptions, so the ICERs based on the committee's preferred assumptions are unknown. The following committee-preferred assumptions aligned with adjustments the EAG made in its base case:

- correction of remaining model errors
- only people with CKD stages 1 to 3 are eligible for treatment with sparsentan (see section 3.10).

The committee decided that further analyses are needed to address the uncertainties in the data. The committee requested the following further analyses:

- using data from SPARTACUS to assess the generalisability of PROTECT (see section 3.6)
- removing or revising the week 36 stopping rule to ensure it reflects how sparsentan would be used in clinical practice (see section 3.11)
- using the PROTECT data for CKD progression in the model as far as possible and supplementing with RaDaR when necessary, for example, in transitions from CKD stage 4 to 5 only (see section 3.12)
- using Pollock et al. (2022) for health state costs with scenarios provided using the costs from the EAG's base case and using all cost categories (see section 3.13)
- correcting the probabilistic sensitivity analysis and providing probabilistic ICERs.

Conclusion

Sparsentan is not recommended

3.18 The committee decided that the cost-effectiveness estimates presented by the company and EAG were uncertain because they did not include all its preferred assumptions. Given the uncertainty, the committee would like to see additional analyses. The committee agreed that it was possible that the cost-effectiveness estimates were above the range that NICE considers a cost-effective use of NHS resources. So, it concluded that it could not recommend sparsentan for treating IgAN.

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 C. 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

Richard Nicholas

Vice-chair, technology appraisal committee C

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.

Aamer Jawed

Technical lead

Michelle Green

Technical adviser

Leena Issa

Project manager

Lorna Dunning

Associate director

ISBN: [to be added at publication]