NICE National Institute for Health and Care Excellence

NICE guidance

Sparsentan for treating primary IgA nephropathy

Technology appraisal guidance
Published: 25 June 2025
Last updated: 9 October 2025

www.nice.org.uk/guidance/ta1074

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Sparsentan can be used as option to treat primary immunoglobulin A nephropathy (IgAN) in adults with a:

- urine protein-to-creatinine ratio (UPCR) of 85 mg/mmol or more, or
- urine protein excretion of 1 g/day or more.

It can only be used if the company provides it according to the commercial arrangement.

1.2 Sparsentan should be stopped after 36 weeks if a person's UPCR:

- is 199 mg/mmol or more, and
- has not reduced by 20% or more since starting sparsentan.

1.3 These recommendations are not intended to affect treatment with sparsentan that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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 must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Sparsentan must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that sparsentan provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

Standard care for primary IgAN includes angiotensin-2 receptor blockers such as irbesartan.

For this evaluation, the company specified that people should stop taking sparsentan if it has not lowered their UPCR (the amount of protein in the urine) enough by 36 weeks. This rule is not included in the licence for sparsentan but reflects how it would be used in the NHS.

Clinical trial evidence shows that sparsentan reduces UPCR more than irbesartan. Evidence also suggests that sparsentan is better at maintaining kidney function than irbesartan, but this is uncertain.

The cost-effectiveness estimates for sparsentan are within the range that NICE considers an acceptable use of NHS resources. So, sparsentan can 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.

Price

2.3 The list price for sparsentan 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. This makes sparsentan available to the NHS with a discount. The size of the discount is commercial in confidence.

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. It also heard additional evidence and reviewed further analyses at its second meeting. 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 lead to 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/minute/1.73 m^2, normal function) to stage 5 (eGFR less than 15 ml/minute/1.73 m^2, 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 long delays in accessing specialist care or transplantation, which can lead to worsening eGFR levels. Between 45% and 70% of people with IgAN develop kidney failure within 10 to 20 years, often needing 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 instead 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 have substantial mental health challenges, including anxiety and depression. This is caused by the uncertainty around disease progression and the lack of specific treatments to slow or prevent this. Current treatments are not effective at slowing or preventing disease progression, which often leads to burdensome interventions such as dialysis and transplantation that are not curative. Corticosteroids, while sometimes used, have limited long-term benefits but can cause substantial side effects, such as mood changes and confusion. Dialysis and transplantation are high-risk, invasive procedures that do not offer a cure. Patient experts expressed concern that a kidney transplantation, 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 that can modify the disease course would be a significant step forward, offering hope for better long-term outcomes. At the second committee meeting, a patient expert highlighted that delaying dialysis by even a few years can substantially improve younger people's lives, citing social and economic benefits. These included better employment prospects and fewer restrictions on daily activities. A clinical expert also emphasised the importance of preserving kidney function to reduce time on dialysis, given IgAN's risk of recurring after a transplant. The committee concluded that IgAN has a substantial physical and psychological burden on people with the condition, 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 lowering proteinuria and controlling blood pressure. They explained that the treatment pathway is closely aligned with the Kidney Disease Improving Global Outcomes 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 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 with 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 (from here, TA937). 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 with 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 with current standard care. This 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 in the NHS. Clinical experts confirmed that irbesartan is commonly used in 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, a randomised, double-blind, phase 3 clinical trial. It 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). 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, and 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%), but 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 10% of people to stop taking sparsentan compared with 9% with irbesartan.

Kidney function from PROTECT

3.6 eGFR shows the rate of kidney function decline over time and was a key secondary outcome included in the PROTECT trial. It is reported as the chronic slope and the total eGFR slope. The chronic slope shows the results excluding the acute phase during the first 5 weeks of treatment where eGFR falls. The clinical experts explained that drugs like sparsentan and irbesartan can temporarily lower the kidney's filtering rate when treatment first starts. This is because they reduce blood pressure within the glomeruli, the kidney's filters. The sparsentan chronic slope showed a statistically significant difference compared with the chronic slope for irbesartan but not for the total slope. At the first meeting, the committee had concerns about using the trial results for projecting long-term outcomes such as ESRD, dialysis, and mortality. This was because of the statistical non-significance of the total eGFR slope. But, clinical experts during the first meeting and consultation responses consistently emphasised that the chronic slope is a more clinically relevant measure for predicting long-term kidney outcomes. This is because it isolates ongoing treatment effects by excluding the acute initial dip in eGFR. The company also stated that this initial effect is captured in its modelling approach. It explained that it applied a unique acute transition matrix in cycle 1, and then after that, there's a chronic transition matrix to inform the remaining cycles. During consultation, the company provided updated 2-year modified intention-to-treat (mITT) analyses. The methods used to calculate these results differed from those used to calculate the results for the first analysis. This is because they included data from all trial participants regardless of whether they stopped treatment or had immunosuppressive therapy. In the analyses presented for the first committee meeting (consistent

with the European Medicines Agency approach) sparsentan had a lower mean reduction in eGFR per year by:

- 1.1 ml/minute/1.73 m² (95%CI 0.1 to 2.1; p=0.037) on the chronic slope, and
- 1.0 ml/minute/1.73 m² (95% CI -0.03 to 1.94; p=0.058) on the total slope.

In the new analyses for the second committee meeting (consistent with the US Food and Drug Administration approach), sparsentan had a lower mean reduction in eGFR per year by:

- 1.3 ml/minute/1.73 m² (95% CI 0.33 to 2.31; p=0.0087) on the chronic slope
- 1.2 ml/minute/1.73 m² (95% CI 0.21 to 2.13; p=0.0168) on the total slope.

The EAG noted these analyses indicated a consistent magnitude of benefit. But, differences existed between the analytical methods of the US Food and Drug Administration and European Medicines Agency, specifically related to how missing data from people who stopped treatment was handled. The EAG thought that it was difficult to say which was the most appropriate analysis without more detail on how the missing data assumptions relate to the reasons for stopping treatment. The committee considered that the updated analyses provided some reassurance of sparsentan's effectiveness compared with the original analyses. But it thought that there was continued uncertainty linked to how each analysis accounted for missing data. The committee noted that the updated model does not rely on the same level of surrogate linkage between UPCR and eGFR that underpinned the original model. The new model draws on data from the UK Registry of Rare Kidney Diseases (RaDaR) for later-stage CKD transitions (see section 3.14 and section 3.15), so the lack of a statistically significant total eGFR slope in PROTECT is less critical. This is because progression beyond CKD stage 3 is now partly informed by real-world evidence. The committee concluded that, in the short term, sparsentan was clinically effective compared with irbesartan, providing meaningful reductions in proteinuria with a similar safety profile. However, the committee considered that considerable uncertainty remained about its longer-term effects on kidney function and progression to ESRD, due to limited follow up.

Concomitant treatments in PROTECT

3.7 People in PROTECT were randomised to have either sparsentan or irbesartan with standard care. Standard care included lipid-lowering medicines, antihypertensive medicines 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 (see section 3.3) and thought that this was not reflected in PROTECT. During the first meeting, the clinical experts advised that an initial data cut is available from the SPARTACUS trial, an ongoing single-arm study in which SGLT2 inhibitors are used with sparsentan. The committee understood that SGLT2 inhibitors would be used as part of standard care as well as sparsentan. But, 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 also noted that it had not been given any evidence on using sparsentan with TR-budesonide (for people with a UPCR 1.5 g/g or more). The clinical experts advised that the using sparsentan with 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 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 with sparsentan.

In response to the draft guidance consultation, the company provided data to address the evidence gap in PROTECT (only a small number of people had SGLT2 inhibitors). This included an interim analysis from SPARTACUS (n=20) that showed a 24-week reduction in urine albumin-to-creatine ratio from baseline of 39.5%. It also included real-world evidence from Schanz et al. (2025), a study that looked at the efficacy of sparsentan combined with SGLT2 inhibitors. It showed a mean reduction in UPCR of 65% (95%CI 56% to 77%). This was compared with the mean reduction in UPCR at 24 weeks of 48.7% from PROTECT. The EAG felt that it was still uncertain whether the same magnitude of benefit observed in PROTECT would persist if both arms also had an SGLT2 inhibitor. The committee acknowledged the new evidence but remained cautious because:

- the sample size was limited

- there was no randomised comparator arm, and
- the SPARTACUS trial reported a different outcome (urine albumin-to-creatine ratio) compared with PROTECT (UPCR).

It thought that uncertainties remained around the magnitude and sustainability of any additive effect. The committee acknowledged that that the real-world data appears to be supportive. But it concluded that there may be differences in the relative treatment effect of sparsentan when used with an SGLT2 inhibitor in NHS practice. So this meant the modelling was associated with some uncertainty.

RASi dose titration

3.8 The dose titration of RASi therapy in PROTECT was higher than in other IgAN studies. In PROTECT, 97% of people in the irbesartan arm were titrated to the maximum recommended dose. 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 compared with the comparator. This was 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 seen 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

3.9 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 analysis 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 the clinical experts preferred to use TR-budesonide and sparsentan together. The committee concluded that a comparison with TR-budesonide was not needed for decision making.

Economic model

Company's modelling approach

3.10 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

3.11 At the first committee meeting, the company's model included people with CKD stages 1 to 4 in the sparsentan treatment arm. This assumed that a proportion of

the initial cohort enter the model in CKD stage 4 and begin treatment. The summary of product characteristics (SmPC) for sparsentan states that because of limited clinical experience, it is not recommended in people with severe kidney disease (CKD stage 4 or 5, defined as eGFR below 30 ml/minute/1.73 m^2). To align with the SmPC, the EAG restricted sparsentan use in its base case to people with CKD stages 1 to 3. The EAG's clinical advisers said that they would adhere to the SmPC by not starting treatment at CKD stage 4. They would also stop treatment in people with sustained eGFR values below 30 ml/minute/1.73 m^2, which suggests progression to CKD stage 4. Clinical experts stated at the first meeting that they would prefer flexibility, to allow people with an eGFR below 30 ml/minute/1.73 m^2 to keep having sparsentan. Based on this information, the committee determined that starting sparsentan in people with CKD stage 4 would be considered off-label. It concluded that the modelling should reflect the marketing authorisation and align with the population in the SmPC, meaning only people with CKD stages 1 to 3 would be eligible for sparsentan.

At the second committee meeting, the company confirmed that the SmPC wording only applies to starting sparsentan in CKD stage 4. It does not apply to continuing treatment in people who progress to CKD stage 4 after starting treatment at an earlier stage. The company stated that it plans to seek a variation to the SmPC wording to explicitly clarify continued use in CKD stage 4, once sparsentan gains full marketing authorisation. In response to the draft consultation, the company updated its model to reflect this clarification. The updated model only allows people with CKD stages 1 to 3 to start treatment with sparsentan, but allows continued use if people progress to CKD stage 4. Clinical experts at the second meeting and in consultation confirmed they would continue to offer sparsentan to people who progress to CKD stage 4 if they are already having treatment. They highlighted that this approach aligns with the Kidney Disease Improving Global Outcomes guidelines and established clinical practice. A patient expert added that, in practice, some people with IgAN are first diagnosed relatively late, often in CKD stage 3 or 4, which further supports continued treatment in CKD stage 4. The EAG accepted this approach and updated its modelling accordingly. The committee felt it would be useful to amend the SmPC wording to clarify that people could continue with sparsentan treatment, but not start it, in CKD stage 4. It thought that stopping people from starting sparsentan in CKD stage 4, but allowing people already having it continue if they progress to CKD stage 4, would likely reflect NHS practice. So,

the committee concluded that this approach was appropriate for decision making.

Stopping rule

3.12 The company's model incorporates a week 36 stopping rule, requiring that people stop taking sparsentan if they have a 'UPCR of 1.76 g/g or more and 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 noted that certain people in the model could have worsening proteinuria but could still be labelled as 'responding' if their UPCR was below 1.76 g/g which it thought brought uncertainty to the stopping rule. The clinical experts advised that treatment decisions should be based on proteinuria reduction. This is 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. But, they also noted that some people with persistent proteinuria may still get benefits from sparsentan, particularly if there is gradual proteinuria reduction or improvements in blood pressure control. Patient experts expressed concerns about the stopping rule. They noted that people may find it hard to understand why their treatment is being stopped, particularly if they see 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 thought that the application of the company's proposed stopping rule in NHS clinical practice would be challenging.

During consultation, the company argued that the stopping rule could be easily implemented because people with IgAN typically have routine monitoring at least 2- to 4-times a year. It also cited a Delphi consensus in which 4 out of 5 clinical experts supported a 20% reduction threshold as clinically meaningful. During the second meeting, a clinical expert explained that proteinuria is routinely measured every 3 months, making it simple to detect non-response. So implementing the

stopping rule at week 36 would be relatively easy. It was also noted that, in the PROTECT trial, a number of people stopped RASi treatment for reasons other than adverse events. This suggested that both clinicians and patients may prefer to explore alternative treatment options rather than continue with a treatment that does not appear effective. A clinical expert confirmed that they would offer any available alternative treatment options if a treatment appeared not to be working. But a patient expert noted concerns about limited alternative treatments and the psychological impact of stopping treatment. The committee expressed concern that introducing a stopping rule that was not tested in PROTECT might risk missing potential benefits for a small group of late responders, and if this was the case then the stopping rule would result in a reduction in costs but not associated efficacy. The committee acknowledged that the stopping rule was implementable in practice (because people with IgAN are already monitored frequently). But it was concerned about whether people with IgAN would actually want to stop treatment, given the lack of other treatment options. It concluded that applying the stopping rule in the modelling was acceptable for decision making but was associated with uncertainty.

CKD transition probabilities

3.13 In the original model submitted for the first committee meeting, transition probabilities between UPCR categories were estimated using data from PROTECT. CKD stage transitions were informed by external data from the UK 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. They noted a well-documented linear relationship between proteinuria reduction and long-term CKD progression, which is independent of treatment mechanism. They also stated that this relationship has been validated using prospective and retrospective data and was instrumental in regulatory approvals, which supports using proteinuria reduction to predict CKD progression. At the first meeting the committee noted that PROTECT showed a statistically significant reduction in proteinuria with sparsentan but did not show a significant impact on total eGFR slope (see section 3.6). 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 using PROTECT are closer to the observed proportion of people in each CKD stage at week 108, than 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).

Updated CKD transition probabilities

3.14 At the second committee meeting, the company confirmed it had implemented the requested hybrid approach for its updated model. CKD transitions for stages 1 to 3 were taken from PROTECT, whereas transitions from stage 4 to

ESRD come from RaDaR. The EAG verified that the company's hybrid transition matrices replace the CKD 4 row of the PROTECT-based matrix with RaDaR data, consistent with the committee's initial request. The EAG noted that overall progression rates still resemble a mostly RaDaR-driven curve (with around 9% to 10% of people reaching ESRD by 2 years in the comparator arm). The clinical experts stated that this would be plausible if many people start near an eGFR of 30 ml/minute/1.73 m^2. The EAG noted that while many people did start treatment with this eGFR, there were also a substantial number of people in the PROTECT trial who started with a higher eGFR (the exact proportions are considered confidential by the company and cannot be reported here). The EAG stated that it was still unclear precisely how the new hybrid transition probabilities were calculated. It acknowledged that the company's updated hybrid approach broadly addressed the committee's request. This included using PROTECT data for early CKD transitions and supplementing with RaDaR data only when necessary. But the EAG reiterated the need for external validation, particularly around the plausibility of 2-year ESRD rates for the IgAN population. The committee acknowledged that the company had provided the analyses requested at the first meeting and agreed this reduced some of its concerns around CKD stage modelling. But it still had concerns around the plausibility of 2-year ESRD rates and the calculation of the RaDaR transition probabilities. The committee concluded that using the hybrid approach for transitions was appropriate but associated with some residual uncertainty.

Costs

Health state costs

3.15 In the original model submitted for the first committee meeting, the company's base-case 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. Because of these concerns, the committee previously concluded that IQVIA-based costs introduced significant uncertainty and were unsuitable for decision making. During the first meeting, as an alternative, 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. Following consultation the company updated the model to use micro-costing based on Kent et al. (2015). This method was used in TA937. The company acknowledged the EAG's criticism of the IQVIA analysis and agreed it was not possible to fully resolve these concerns. The company also questioned the face validity of the broader Pollock et al. cost categories. It pointed out implausible anomalies such as people with CKD stage 1 and 2 with high proteinuria incurring higher costs than those awaiting dialysis. It highlighted additional mapping issues between the Pollock et al. data and the modelled health states as their rationale to use the micro-costing approach. The EAG accepted that the micro-costing approach had precedent from TA937, making it a reasonable alternative, but noted its limitations. It highlighted that micro-costing is based on broader CKD categories (grouped CKD stages 1 to 3, and stages 4 and 5) without differentiation by proteinuria level, potentially reducing granularity. This means the model cannot account for the company's and clinical experts' view that higher proteinuria can drive additional costs and worsen quality of life even within the same CKD stage. The committee previously requested scenarios exploring both EAG's base case and broader Pollock et al. costs. The committee noted the continued methodological and validity concerns raised during consultation about Pollock et al. and the ruled out IQVIA costs. So it agreed that the micro-costing approach (Kent et al. 2015) from TA937 was an acceptable alternative. The committee noted that despite its simplicity and the lack of proteinuria-specific costs, and taking into account the limitations around granularity, it was likely to be appropriate for decision making. The committee concluded that the micro-costing approach represented the most pragmatic and justified choice, particularly in the absence of IgAN-specific costing studies.

Other factors

Equality

3.16 During both meetings the committee noted that IgAN disproportionately affects certain ethnic groups, particularly Asian and Black ethnicities. 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 kidney transplantation is often more challenging for these groups, with longer waiting times for donor matches and other barriers to transplantation, which may result in prolonged dependence on dialysis. Race is a protected characteristic under the Equality Act 2010. The committee considered whether faster disease progression and limited access to transplantation among Asian and Black populations might require separate or targeted recommendations. The committee noted that issues of differing disease prevalence in groups with protected characteristics cannot be addressed through a technology appraisal. Clinical experts clarified that transplantation is not a definitive solution for IgAN, as the disease can recur after a transplant. The committee concluded that there was insufficient evidence to conclude that a positive recommendation would disproportionately disadvantage any groups with protected characteristics.

Uncaptured benefits

3.17 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. They also noted that it can cause 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 a kidney transplant, face cumulative risks of cancer and other adverse effects. This reinforces the need for additional treatment options that can delay progression to ESRD. Clinical and patient experts also highlighted that the demand for renal services is increasingly impacting the availability of dialysis and waiting times for transplants. So, a treatment that could preserve kidney function would be valuable. During the second meeting a clinical expert explained that IgAN often recurs after transplant, so delaying progression to ESRD and extending time off dialysis is particularly valuable. The committee recognised these issues and concluded that there were uncaptured benefits of sparsentan to consider in its decision making.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.18 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 (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:

- there was ongoing uncertainty about the longer-term effectiveness of sparsentan data from PROTECT, so there is uncertainty in the longer-term outcomes used in the model (see section 3.6)
- PROTECT did not evaluate sparsentan or irbesartan with SGLT2 inhibitors (see section 3.7)
- dose titration in PROTECT was higher and happened more quickly than is expected in the NHS (see section 3.8)
- a stopping rule is applied at week 36 in the model and in practice but was not present in the trial (see section 3.12)

- CKD transition probabilities from the hybrid approach may model implausibly high numbers of people in ESRD at 2 years (see section 3.13 and section 3.14)
- health state costs based on the micro-costing approach do not account for differences in UPCR (see section 3.15).

The committee also considered the unmet need (see section 3.2) and the uncaptured benefits of sparsentan (see section 3.17). Given the level of uncertainty the committee concluded that an acceptable ICER would be about £20,000 per QALY gained.

Committee preferred cost-effectiveness estimates

3.19 The exact cost-effectiveness estimates cannot be reported here because there are confidential discounts for sparsentan. The committee's preferred cost-effectiveness estimates included the following assumptions:

- remaining model errors corrected and probabilistic ICERs used
- treatment with sparsentan only started in CKD stages 1 to 3 but treatment allowed to continue if people progress to CKD stage 4 (see section 3.11)
- PROTECT data used for CKD transitions from CKD stages 1 to 3, supplemented by RaDaR data for CKD stage 4 onwards (see section 3.13 and section 3.14)
- a stopping rule applied at 36 weeks (see section 3.12)
- Kent et al. (2015) used for health state costs as per TA937 (see section 3.15).

Conclusion

Recommendation

3.20 The committee took into account its preferred assumptions and the key uncertainties in the model. It concluded that the most plausible ICER for

sparsentan compared with irbesartan was within the range that NICE usually considers an acceptable use of NHS resources. So, sparsentan is recommended for treating IgAN.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has immunoglobulin A nephropathy and the healthcare professional responsible for their care thinks that sparsentan is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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 and Samuel Slayen
Technical advisers

Leena Issa
Project manager

Lorna Dunning
Associate director

6 Update information

October 2025: We updated recommendations 1.1 and 1.2 to change the unit for urine protein-to-creatinine ratio (UPCR) to mg/mmol from g/g. A UPCR of 85 mg/mmol or more equates to the 0.75 g/g or more measurement specified in the marketing authorisation indication for sparsentan. A UPCR of 199 mg/mmol or more equates to 1.76 g/g or more.

ISBN: 978-1-4731-7243-2