NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Targeted-release budesonide for treating primary IgA nephropathy (review of TA937)

1 Recommendations

1.1 Targeted-release budesonide can be used as an option to treat primary immunoglobulin A nephropathy (IgAN) in adults when:

- they have:
  - a urine protein-to-creatinine ratio (UPCR) of 90 mg/mmol or more or
  - a protein excretion of 1.0 g/day or more, and
- it is used as an add-on to optimised standard care that includes, unless contraindicated:
  - the highest tolerated licensed dose of renin-angiotensin system inhibitors (RASi) or
  - a dual endothelin angiotensin-receptor antagonist (DEARA), and
- the company provides it according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with targeted-release budesonide 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

Targeted-release budesonide 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. Targeted-release budesonide must be funded in England within 90 days of final publication of this guidance.

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

Why these recommendations were made

This evaluation reviews the evidence for targeted-release budesonide for treating primary IgAN (NICE technology appraisal guidance 937). It considers use of targeted-release budesonide in a broader population than it was recommended for in TA937, including using a lower UPCR threshold.

Usual treatment for primary IgAN includes optimised standard care. This has changed since the previous evaluation and now includes RASi or DEARA, with or without a sodium-glucose cotransporter-2 inhibitor (SGLT2i). Targeted-release budesonide is used as an add-on to optimised standard care.

Clinical trial evidence shows that targeted-release budesonide plus optimised standard care increases how long people have before their condition gets worse compared with optimised standard care alone.

There are uncertainties in the economic model. This is because standard care in the trial did not include DEARA or SGLT2i treatments, which are currently used in the NHS.

But, the most likely cost-effectiveness estimates are below the range that NICE considers an acceptable use of NHS resources. So, targeted-release budesonide can be used.

For all the evidence, see the committee papers. For more information on streamlined evaluations, see NICE's manual on health technology evaluations.

2 Information about targeted-release budesonide

Marketing authorisation indication

2.1 Targeted-release budesonide (Kinpeygo, Genus Pharmaceuticals) 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 ≥0.8 g/gram)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for targeted-release budesonide (PDF only).

Price

2.3 The list price of targeted-release budesonide is £4,681.24 for a 120-pack of 4-mg modified-release hard capsules.

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes targeted-release budesonide available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

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

3 Committee discussion

The evaluation committee considered evidence submitted by Genus Pharmaceuticals, 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.

Clinical management

Eligible population

3.1 This evaluation is a review of NICE technology appraisal guidance on targeted-release budesonide for treating primary IgA nephropathy (from here referred to as TA937). TA937 recommended targeted-release budesonide for treating primary immunoglobulin A nephropathy (IgAN) as an add-on to standard care. It was recommended for adults who have a risk of rapid disease progression and a urine protein-to-creatinine ratio (UPCR) of 170 mg/mmol or more (equivalent to a UPCR of 1.5 g/g or more). The recommendation stipulated that optimised standard care included the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), unless they are contraindicated. This review considered an expanded marketing authorisation indication. It stipulates that targeted-release budesonide is used as an add-on to standard care in adults with IgAN and a UPCR of 90 mg/mmol (equivalent to a UPCR of 0.8 g/g or more) or a urine protein excretion of 1 g/day or more.

The committee heard from clinical experts and professional organisations that reducing the threshold UPCR for access to targeted-release budesonide would allow more proactive management of IgAN. Patient experts commented that preventing disease progression and delaying the need for dialysis or kidney transplant are particularly important, and that people with IgAN would welcome earlier access to targeted-release budesonide. The committee concluded that widening access to targeted-release budesonide would be welcomed by healthcare professionals and people with IgAN.

Treatment pathway

3.2 Clinical experts explained that the treatment pathway for IgAN is closely aligned with the Kidney Disease Improving Global Outcomes (KDIGO) 2025 Clinical practice guideline for the management of immunoglobulin A

nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV) (PDF only; from here referred to as the KDIGO guideline). In the KDIGO guideline, people with IgAN who are at risk of progressive loss of kidney function requiring treatment, are defined as those with a urine protein excretion of 0.5 g/day or more (or equivalent). The KDIGO guideline recommends that:

- IgAN-specific immunological drivers for nephron loss should be managed with targeted-release budesonide or systemic glucocorticoids
- for managing the generic responses to IgAN-induced nephron loss and to reduce associated cardiovascular risk, the following should be offered, with or without a sodium-glucose cotransporter 2 inhibitor (SGLT2i):
  - RASi (which are ACE inhibitors and ARBs), or
  - a dual endothelin angiotensin-receptor antagonist (DEARA), such as sparsentan.

The KDIGO guideline also recommends that standard care includes lifestyle advice for adults with IgAN, such as dietary interventions. The committee concluded that for treating IgAN, targeted-release budesonide would be used as an add-on to standard care.

Standard care in the model

3.3 Standard care was included in the model in both the intervention arm (with add-on targeted-release budesonide) and the comparator arm (on its own). But the company's definition of standard care was narrower than the definition in the KDIGO guideline (see section 3.2) and the NICE scope. The NICE scope included the following SGLT2is as options to treat chronic kidney disease in adults:

- dapagliflozin (see NICE's technology appraisal guidance on dapagliflozin for treating chronic kidney disease, from here referred to as TA1075) and
- empagliflozin (see NICE's technology appraisal guidance on empagliflozin for treating chronic kidney disease, from here referred to

as TA942).

In the model, the cost of dapagliflozin treatment was included within standard care costs. The committee noted that the effectiveness of the SGLT2is was not modelled because these treatments were not a component of standard care in the trial (see section 3.4). Clinical expert advice to the EAG was that around 70% of people with IgAN are expected to have an SGLT2i as part of standard care in clinical practice. The NICE scope also included the DEARA sparsentan as a component of standard care, subject to a NICE evaluation. NICE recently recommended sparsentan as an option for treating IgAN (see NICE's technology appraisal guidance on sparsentan for treating primary IgA nephropathy). The committee recalled that the KDIGO guideline included DEARA as an alternative to RASi. This is because sparsentan combines RASi with an endothelin antagonist in a single molecule. Clinical expert advice to the EAG was that sparsentan is likely to replace RASi in NHS clinical practice. But less was known about sparsentan's use because it was only recently recommended for routine commissioning. The committee noted the view from a clinical expert that newer standard care treatments may provide greater slowing of disease progression (slower loss of estimated glomerular filtration rate [eGFR]) than RASi alone. But it understood that this potential effect would likely be modest and less than that of controlling the immunological aspect of IgAN with targeted-release budesonide. The committee noted exploratory analyses done by the EAG that considered the potential impact of improved standard care effectiveness (see section 3.7 and section 3.13). The committee concluded that standard care in the model was narrower than the NICE scope and the KDIGO guideline, which created uncertainty. It also concluded that while newer standard care treatment might provide greater slowing of disease progression than the rate in the model, this effect was likely to be modest. So overall, the company's modelling of

standard care was acceptable for decision making despite the uncertainty.

Clinical effectiveness

Key clinical trial

3.4 NeflgArd Nef 301 was a multinational, randomised, double-blind, multicentre clinical trial. It compared targeted-release budesonide plus standard care, including maximally tolerated RASi therapy with an ACE inhibitor or ARB, with standard care plus placebo. The trial had a 2-part design:

- part A comprised a 9-month treatment period with a 3-month follow up, and
- part B comprised an additional no-treatment 12-month follow-up period.

The main clinical evidence in the company's submission for this review of TA937 was from part B of the trial (n=364). There was also a single-arm, open label extension (OLE) of NeflgArd Nef 301 (n=119). In the OLE, people had targeted-release budesonide as retreatment (see section 3.10) or as a first round of treatment after placebo in the 2-arm trial. NeflgArd Nef 301 and the OLE included people with proteinuria of 1 g/day or more or a UPCR of 0.8 g/g or more (equivalent to 90 mg/mmol or more). People also had an eGFR of:

- between 35 ml/minute/1.73 m^2 and 90 ml/minute/1.73 m^2 in NeflgArd Nef 301 and
- 30 ml/minute/1.73 m^2 or more in the OLE.

IgAN had to be stable on a maximum-tolerated dose of an ACE inhibitor or ARB for 3 months before randomisation, unless contraindicated. Optimised, stable RASi therapy continued throughout the trial and OLE. The committee noted that SGLT2i and sparsentan were not an established part of standard care when the trial was done.

It recalled exploratory analyses done by the EAG that considered the potential impact of improved standard care effectiveness in the model (see section 3.7 and section 3.13). The committee concluded that it was satisfied that the trial evidence for targeted-release budesonide was broadly generalisable to people who would have treatment in the NHS, although the trial did not include some current NHS treatments.

Outcomes and results

3.5 The primary outcome in part B of the trial was time-weighted average of eGFR at each time point over 2 years. Change in UPCR and eGFR at 9 months after the first dose compared with baseline was the primary outcome of the OLE, including for retreatment. Trial part B results showed that, compared with placebo, 9 months of targeted-release budesonide treatment slowed the decline of eGFR and produced a durable reduction in proteinuria over 2 years. The average eGFR decline over 2 years was 2.47 ml/minute/1.73 m^2 (95% confidence interval [CI] 3.88 to 1.02) with targeted-release budesonide and 7.52 ml/minute/1.73 m^2 (95% CI 8.83 to 6.18) with placebo. The committee concluded that targeted-release budesonide showed a clinical benefit in reducing chronic kidney disease progression associated with IgAN when used as an add-on to standard care in the trial.

Economic model

Company's modelling approach

3.6 The company used a cohort-level state transition model with 6 health states. These were defined according to chronic kidney disease (CKD) stages 1 to 5 (including stages 3a and 3b) with additional states for dialysis, kidney transplant and death. The CKD health states were populated using the baseline distribution of CKD stages from NefIgArd Nef 301 part B. The committee noted that the structure and modelling assumptions, including for health state utilities and costs, were consistent with those accepted in TA937 and TA1075, except where there was new

evidence. The committee concluded that the company's model structure and overall approach was appropriate.

Transition probabilities for CKD stages 1 to 4

3.7 People in CKD health states 1 to 4 could transition to improved or worsened neighbouring health states. From 0 months to 24 months, transition probabilities were derived from the eGFR results for the 2 arms of the clinical trial (see section 3.5). The company used a logistic regression model fitted to baseline and 24-month trial individual patient data. Log odds were converted to 24-month probabilities, from which monthly transition probabilities were derived. After 24 months, the CKD 1 to 4 transition probabilities observed in the trial for people having placebo were applied to both arms of the model. So, targeted-release budesonide was modelled to have a treatment effect lasting up to 2 years only. The EAG thought that the company's methods for estimating transition probabilities for CKD 1 to 4 were appropriate. But it noted there was high uncertainty due to sparse data for some transitions. It suggested that an alternative modelling of transition probabilities for standard care could be useful. The suggested approach would be based on a large dataset reflective of current practice (for example Inker et al. 2019 and Barratt et al. 2024), with the treatment effect from the trial applied. But the EAG was unclear whether this approach would reduce the uncertainty. The EAG also explained that the impact of changes to standard care in NHS clinical practice on the modelled treatment effect of targeted-release budesonide was unknown. The EAG explored the sensitivity of the model results to reduced disease progression on standard care treatments by applying progression multipliers of less than 1.0 to both arms. The committee understood that assuming standard care was more effective reduced the cost effectiveness of targeted-release budesonide (see section 3.13). It recalled that newer standard care treatments may provide greater slowing of disease progression than those used in the clinical trial, but this would likely be a modest effect (see section 3.3). So, the committee decided that the modelling should incorporate a small

reduction in standard care progression (by applying a 0.90 factor to both arms). The committee decided that the company's approach to modelling transition probabilities for CKD health states 1 to 4, based on the trial evidence, was reasonable. It concluded that there was high uncertainty due to sparse data for some transitions. It also concluded that it preferred to incorporate a small reduction in disease progression for standard care in both arms, to reflect the availability of newer treatments in clinical practice.

Transition probabilities for CKD stage 5 and beyond

3.8 The company explained that people with CKD stage 4 were not eligible for NefIgArd Nef 301, so the transition probability from CKD stage 4 to CKD stage 5 was informed by alternative evidence. For the standard care alone arm, the risk of entering CKD stage 5 was based on real-world data on people with IgAN and a UPCR of 0.8 g/g or more. The data was taken from the UK National Registry of Rare Kidney Diseases (RaDaR). A hazard ratio (HR) for progression of 0.38 was then applied for the targeted-release budesonide arm with a 2-year duration of effect. This HR was from an eGFR slope-modelling study of targeted-release budesonide (Barratt et al. 2024). The EAG thought that this was a reasonable approach. To explore uncertainty in the treatment effect for risk of CKD 5, the EAG's applied the upper and lower 95% CIs around the HR. The 95% CIs were assumed to be the same for targeted-release budesonide and standard care and were from the economic model in TA1075. The committee concluded that the company's approach to modelling transition probabilities from CKD stage 4 to CKD stage 5 and from CKD stage 5 to dialysis and transplant was reasonable.

Mortality

3.9 Risk of death was based on standardised mortality ratios from the UK RaDaR dataset. The EAG noted that in the values applied in the company's model, mortality was lower in health states CKD 3a and 3b, compared with CKD 2. The EAG preferred to adjust the mortality values

for CKD stages 3a and 3b by setting them equal to CKD 2. This adjustment meant that mortality was not lower in more advanced disease. The committee concluded that it preferred the EAG's approach for mortality.

Assumptions about retreatment

3.10 The marketing authorisation for targeted-release budesonide states that retreatment may be considered at the discretion of the treating healthcare professional. But, the safety and efficacy of retreatment has not been established. The company presented evidence from the Nef-301 OLE, in which 45 people had 1 round of retreatment plus 3 months of follow up. In the company's modelling of retreatment:

- A proportion of people who finished their initial course of targeted-release budesonide and still had CKD stages 1 to 3b were expected to have retreatment within their lifetime. The proportion was based on eligibility for retreatment in the OLE and is considered confidential by the company. The company noted that the model assumed that people whose IgAN had not responded to initial treatment would not have retreatment with targeted-release budesonide.
- One round of retreatment (2 treatment rounds in total) was included. The company explained this was a conservative assumption because people are not expected to develop treatment resistance or effect waning.
- Retreatment had 90% of the treatment effect from the first course of targeted-release budesonide. The company explained that this was considered conservative because the OLE study showed that the effectiveness of targeted-release budesonide in retreatment was similar to that in initial treatment.

The EAG agreed with the company that its retreatment assumptions were appropriate for use in the economic model but noted that there was still uncertainty around them. The committee noted that the company and

EAG considered that the OLE study had an overall serious risk of bias. It also noted that there was only evidence from the OLE for 1 round of retreatment with targeted-release budesonide and that there was only 3 months of follow up. The committee considered scenario analyses from the company and EAG exploring different retreatment assumptions. These were for the proportion of people who had retreatment, number of retreatment rounds, time between rounds and effectiveness of retreatment. The EAG explained that including additional rounds of treatment in the model meant that targeted-release budesonide becomes more cost saving. This was because people stayed in the lower CKD health states for longer. This meant they avoided progressing to higher CKD health states that have much higher treatment costs caused by the increasing frequency of dialysis and kidney transplants. These cost savings were greater than the drug costs for including additional rounds of treatment. The committee concluded that it was satisfied with the retreatment assumptions used in the company's model. It also concluded that there is uncertainty around the health benefits and cost effectiveness of repeated rounds of retreatment. But it also concluded that additional rounds of retreatment suggest improved cost effectiveness of targeted-release budesonide.

Costs

Stopping treatment, dosing and wastage

3.11 The marketing authorisation for targeted-release budesonide states that when treatment is stopped, the dosage should be reduced to 8 mg once daily for 2 weeks. It may then be reduced to 4 mg once daily for an additional 2 weeks at the discretion of the treating healthcare professional. The company acknowledged that the timing of stopping, whether it was within or after the 9-month treatment duration, was open to clinical decision making. It explained that in the model, stopping was assumed to occur as part of the 9-month treatment duration and that the dosage was reduced to 8 mg once daily for 2 weeks. The EAG noted that the cost of targeted-release budesonide wastage was impacted by the timing of

stopping when considering the standard 120-pack of 4-mg modified-release hard capsules. The company clarified that it expected wastage of targeted-release budesonide to be minimal because a smaller 28-pack size had recently been introduced at a pro-rata price. The EAG was satisfied that this new pack size would reduce the wastage costs. The committee noted that scenarios exploring alternative assumptions for the timing of stopping, tapering and dose intensity had a small impact on the cost-effectiveness results. The committee concluded that the company's modelling of treatment stopping was reasonable. It also concluded that there is uncertainty around stopping targeted-release budesonide and associated wastage in clinical practice, but this is expected to have a small impact on overall treatment costs.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.12 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:

- the trial evidence used in the model did not capture the effectiveness of newer standard care treatments
- there was sparse data underlying some transition probabilities between CKD stages 1 to 4
- there was limited evidence to inform the assumptions about retreatment with targeted-release budesonide.

So, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained.

Committee preferred assumptions

3.13 The committee considered the cost effectiveness of targeted-release budesonide plus standard care compared with standard care alone in people with a urine protein excretion of 1.0 g/day or more (or a UPCR of 0.8 g/g or more). In the company's deterministic model, targeted-release budesonide plus standard care was less costly and more effective than standard care alone (that is, targeted-release budesonide was dominant). The company's probabilistic ICER was £1,211 per QALY gained. The committee noted that the EAG corrected minor standard care cost errors in the company's base case model and used adjusted values for mortality (see section 3.9). Using these corrections, targeted-release budesonide was dominant in the EAG's deterministic and probabilistic base cases. The committee recognised that standard care in the company model did not include the effectiveness of SGLT2is or sparsentan (see section 3.3 and section 3.4). So, the committee's preferred approach was to use the EAG base case analyses but to also apply a 0.9 multiplier for standard care progression in both arms. This resulted in a committee's preferred ICER (deterministic) for targeted-release budesonide of £1,950 per QALY gained.

The committee concluded that the most likely cost-effectiveness estimate for targeted-release budesonide plus standard care compared with standard care alone, was likely to be under £20,000 per QALY gained. So, it was within the range that NICE considers an acceptable use of NHS resources.

Other factors

Equality

3.14 The committee did not identify any equality issues.

Conclusion

Recommendation

3.15 The committee concluded that targeted-release budesonide taken as an add-on to optimised standard care was likely to be a cost-effective use of NHS resources compared with standard care alone. It noted uncertainty in the modelling of standard care, including that DEARA and SGLT2i were not included in the clinical trial. But it concluded that the most likely cost-effectiveness estimate was below the range that NICE considers an acceptable use of NHS resources. So targeted-release budesonide is recommended as an add-on to optimised standard care for treating primary IgAN in adults with a urine protein excretion of 1.0 g/day or more (or a UPCR of 90 mg/mol or more).

4 Implementation

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.

4.1 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.

4.2 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 primary IgAN and the healthcare professional responsible for their care thinks that targeted-release budesonide 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 5 technology appraisal committees are standing advisory committees of NICE. This topic was considered as a streamlined evaluation by the lead team of the highly specialised technologies evaluation committee, which includes the chair.

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

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

Chair

Paul Arundel
Chair, highly specialised technologies evaluation committee

NICE project team

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

Catherine Spanswick
Technical lead

Alan Moore
Technical adviser

Thomas Feist

Project manager

Richard Diaz

Associate director

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