NICE National Institute for Health and Care Excellence

NICE guidance

Targeted-release budesonide for treating primary IgA nephropathy

Technology appraisal guidance
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www.nice.org.uk/guidance/ta937

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 Targeted-release budesonide is recommended as an option for treating primary immunoglobulin A nephropathy (IgAN) when there is a risk of rapid disease progression in adults with a urine protein-to-creatinine ratio of 170 mg/mmol or more. Targeted-release budesonide is recommended only if:

- it is an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated
- the company provides it according to the commercial arrangement.

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 clinician consider it appropriate to stop.

Why the committee made these recommendations

Standard care for IgAN includes lifestyle and dietary changes, and ACE inhibitors or ARBs. Targeted-release budesonide would be used as an add-on to optimised standard care with ACE inhibitors or ARBs.

Clinical trial evidence suggests that targeted-release budesonide plus standard care is more effective than standard care alone. Also, it is the first licensed treatment that specifically treats the condition, increasing the likelihood that people may avoid or delay the need for dialysis or a kidney transplant.

The most likely cost-effectiveness estimate for targeted-release budesonide is within the range that NICE considers an acceptable use of NHS resources. So it is recommended.

2 Information about targeted-release budesonide

Marketing authorisation indication

2.1 Targeted-release budesonide (Kinpeygo, Britannia) is indicated for 'the treatment of primary immunoglobulin A (IgA) nephropathy (IgAN) in adults at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/gram'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of targeted-release budesonide is £6,528.54 for a 120-pack of 4-mg modified-release hard capsules.

2.4 The company has a commercial arrangement. This makes targeted-release budesonide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Britannia, 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). It is caused by IgA antibodies building up in the kidney causing inflammation and scarring, which can lead to kidney failure (end-stage renal disease). In primary IgAN there is no obvious initiating or underlying cause, but genetic and environmental factors such as exposure to toxins are thought to be contributing factors in some cases. Disease progression is defined by estimated glomerular filtration rate (eGFR)-based CKD stages. The eGFR shows how well the kidneys are filtering waste products from the body. eGFR is categorised from stage 1 (eGFR of more than 90 ml/min/1.73 m^2), defined as no reduction in kidney function, to stage 5 (eGFR of less than 15 ml/min/1.73 m^2), defined as kidney failure. Progression to kidney failure typically happens at a substantially earlier age with IgAN than other types of CKD, although the disease can be highly variable. In most people, IgAN progresses to kidney failure within 10 to 15 years after diagnosis, with higher proteinuria (high levels of protein in urine) being a key risk factor for faster progression. The degree of proteinuria is usually defined by urine protein-to-creatinine ratio (UPCR).

Effects on quality of life

3.2 Patient experts highlighted that IgAN can have huge effects on a person's quality of life. They explained that IgAN can have a broad range of symptoms such as bone and joint pain, fatigue and muscle weakness. As the condition progresses, CKD and associated infections can lead to hospitalisation or emergency

department visits. A high risk of certain comorbidities has also been reported for people with IgAN, including an increased risk of future ischaemic heart disease. They also explained that IgAN affects mental health and emotional wellbeing, particularly because there are currently no disease-modifying treatments to slow or prevent the inevitable decline in kidney function. People with IgAN can spend a significant amount of time in hospital, especially when having dialysis. This can substantially limit the person's capacity to stay in work, maintain relationships and fulfil day-to-day responsibilities without support. A kidney transplant is an option for people with IgAN, but this is a highly invasive procedure and is also not curative. Patient experts stated that preventing disease progression and delaying the need for dialysis and a kidney transplant are particularly important, and people with IgAN would welcome a new treatment option. The committee noted that even with current best practice, IgAN can often progress to end-stage kidney disease. The committee concluded that IgAN is a significant burden for people and can substantially affect both physical and psychological aspects of quality of life.

Clinical management

Standard care as a comparator

3.3 The patient and clinical experts highlighted that there is no available cure for IgAN, and that there are limited pharmacological options to delay disease progression. The clinical experts explained that available treatments aim to control blood pressure and reduce proteinuria to slow the rate of kidney function decline. They explained that the treatment pathway is closely aligned with the Kidney Disease Improving Global Outcomes (KDIGO) 2021 Guideline for the Management of Glomerular Diseases. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), which are both types of renin-angiotensin-system inhibitors (RASi), are standard care for IgAN and can slow the rate of disease progression. The KDIGO guideline also recommends that standard care includes lifestyle advice for adults with IgAN, including dietary interventions. The committee noted that while sodium-glucose cotransporter-2 (SGLT2) inhibitors and statins may be used for IgAN, these are for controlling cardiovascular risk associated with the condition. The clinical experts stated that,

in some people, SGLT2 inhibitors would be used alongside targeted-release budesonide because they have a different mechanism of action. In its evidence submission the company positioned targeted-release budesonide as an add-on treatment to optimised standard care, including maximally tolerated RASi therapy with either an ACE inhibitor or ARB. The clinical experts agreed that targeted-release budesonide would be used in addition to standard care including optimised RASi therapy and SGLT2 inhibitors for some people. The committee concluded that it was appropriate to compare targeted-release budesonide as an add-on to standard care with standard care alone.

Corticosteroids

3.4 Systemic corticosteroids, such as prednisolone, can be used to treat IgAN. But the clinical experts explained that these are infrequently used in the UK because they have an unfavourable risk to benefit profile. A patient expert further explained that systemic corticosteroids are associated with side effects that can have a substantial effect on quality of life, and that most people with IgAN are very keen to avoid having them. The clinical experts stated that the KDIGO guideline recommends that systemic corticosteroids should only be considered when people with IgAN continue to have a high risk of disease progression despite having optimised standard care and there is no available clinical trial that could offer an alternative treatment option. They explained that the risk to benefit profile of systemic corticosteroids means that they are only suitable for people with the most severe symptoms, and that most nephrologists in the UK do not use them for treating IgAN. The committee noted that the KDIGO guideline highlights an important risk of treatment-emergent toxicity and states that the clinical benefit of systemic corticosteroids for IgAN is not established. The committee heard that, if used, prednisolone would be the preferred systemic corticosteroid.

Targeted-release budesonide and relevant comparators

3.5 The committee was aware that targeted-release budesonide is a type of corticosteroid, formulated with the expectation that it is mainly released in the terminal ileum (the final section of the small intestine). It reduces IgA production

at this site and is not absorbed systemically to the same extent as prednisolone. The committee noted that targeted-release budesonide is expected to have the same spectrum of adverse effects as prednisolone, albeit at a lower frequency. The clinical experts explained that indirect estimates suggest that the amount of targeted-release budesonide that is absorbed systemically is equivalent to 5 to 7 mg of prednisolone, whereas prednisolone would usually be given at a dose of 40 to 60 mg for IgAN. For this reason, the clinical experts suggested that the serious side effects of prednisolone such as loss of bone mineral density are not expected with targeted-release budesonide, but would be closely monitored. The committee noted that there are other controlled-release formulations of budesonide available for different conditions such as Crohn's disease, which are released in different sections of the gut. The clinical experts stated that these formulations are not used off-label for IgAN because there is no published evidence on their efficacy for this condition. The experts stated that all formulations have different patterns of drug release in the body, and that where the drug is released is critical to its clinical effectiveness and side effect profile. The committee was also aware that the immunosuppressant mycophenolate mofetil (MMF) is rarely used in clinical practice in the UK because of a lack of evidence on its efficacy for IgAN. The committee was satisfied that MMF was not part of standard care and so was not a relevant comparator, but prednisolone could be considered as a relevant comparator because it is occasionally used. The committee reiterated its conclusion that standard care was the relevant comparator for targeted-release budesonide, but accepted that for some people this could also include prednisolone. It further concluded that other controlled-release formulations of budesonide are not relevant comparators. However, a committee member noted a small retrospective observational study of gastro-resistant budesonide (Budenofalk) done in Romania. This concluded that it was more effective than systemic steroids in people with IgAN over 24 months of treatment (Ismail et al. 2020). The committee agreed that it is clinically plausible that other controlled-release formulations of budesonide could be effective for IgAN and that further research on this would be valuable.

Clinical effectiveness

Key clinical trial

3.6 The main clinical evidence in the company's submission was from NefIgArd Nef-301 (n=197). This was a multinational, randomised, double-blind, multicentre clinical trial comparing targeted-release budesonide plus standard care, including maximally tolerated RASi therapy with an ACE inhibitor or ARB, to standard care plus placebo. The trial had a 2-part design: part A included a 9-month treatment period with a 3-month follow up, and part B comprised an additional no-treatment follow-up period of 12 months. NefIgArd Nef-301 included people with proteinuria of 1 g/day or more or a UPCR of 0.8 g/g or more (90 mg/mmol or more). People also had an eGFR between 35 and 90 ml/min/1.73 m^2. IgAN had to be stable on a maximum tolerated dose of an ACE inhibitor or ARB for 3 months before randomisation, unless medically contraindicated. The population of interest in the company evidence submission was a subgroup of people with a baseline UPCR of 1.5 g/g or more, reflecting those at risk of rapid disease progression. The primary outcome in the trial was the change in UPCR from baseline at 9 months of treatment compared with placebo. The change in eGFR from baseline at 9 and 12 months compared with placebo was a secondary outcome and was used in the company's economic model. The committee was aware that the company provided up to 12 months of data from part A of NefIgArd Nef-301 in its evidence submission. Longer follow-up data to 24 months from part B of the trial, which also included more people, was provided at technical engagement. The results of the trial are confidential and cannot be reported here. But overall, targeted-release budesonide showed benefit on UPCR and eGFR at 9 months compared with placebo, and that this benefit is maintained after stopping treatment. The committee agreed that the subgroup of people with a baseline UPCR of 1.5 g/g or more was appropriate for its decision making because it reflected the licensed population for targeted-release budesonide. It concluded that targeted-release budesonide showed a clinical benefit for this subgroup. The committee noted that targeted-release budesonide was used as an add-on to standard care in the trial, and that its decision would depend on it being used in this way in clinical practice.

Generalisability of evidence: RASi therapy

3.7 The committee recalled that people in NefIgArd Nef-301 were on maximally tolerated RASi therapy with either an ACE inhibitor or an ARB. The EAG explained that 6 people in the subgroup with a baseline UPCR of 1.5 g/g or more were not having either one of these treatments. It explained that this is in line with the trial entry criteria because a maximally tolerated dose can be no dose if these drugs are not well tolerated. The EAG cautioned that the evidence from NefIgArd Nef-301 may not be applicable to the population who would be seen in UK clinical practice who are not having RASi therapy. This is because 6 people is too few to make robust conclusions on the effectiveness of targeted-release budesonide in this population. The company and clinical experts explained that people with IgAN who cannot tolerate RASi therapy have very limited treatment options. The clinical experts agreed that for some people these treatments are not well tolerated, but that in practice all people with IgAN would be having RASi therapy if they can tolerate it. Also, the number of people with IgAN who are not having RASi therapy is very low, estimated to be in the region of 1%. The clinical experts added that there is no reason to suspect that targeted-release budesonide would not be equally effective in the very small population who are not having RASi therapy because the mechanisms of action for the 2 treatments are very different. The committee recalled that targeted-release budesonide would always be used as an add-on to maximally tolerated RASi therapy, because occasionally the highest tolerated dose will be no dose.

Generalisability of trial population

3.8 The company explained that the demographic and disease characteristics of the trial population broadly reflected the characteristics of the UK target population, and this was confirmed by UK clinical expert opinion. It further supported its claim with reference to demographic and disease characteristics data from the UK National Registry of Rare Kidney Diseases (RaDaR) database. The EAG agreed that the trial population was broadly generalisable. But it highlighted that there was some lack of detail in important variables in the company's comparison with the RaDaR data, and that only some of the variables were compared. A committee member noted that the reported ratio of men to women with IgAN showed geographical variability. A clinical expert confirmed that in Western

countries the ratio of men to women with IgAN is around 2 to 1; whereas in Eastern countries there tends to be equal numbers of men and women with the condition. But the clinical experts explained that the NefIgArd Nef-301 population had the same characteristics as the population seen in UK clinical practice, and that the levels of baseline proteinuria are the same across both populations. They further commented that gender and ethnicity are not considered to be factors that influence the effectiveness of targeted-release budesonide. The committee concluded that the clinical-effectiveness estimates based on NefIgArd Nef-301 were generalisable to the population who would have TRF-budesonide in clinical practice in the NHS.

Indirect treatment comparison

3.9 The committee recalled its consideration of relevant comparators for targeted-release budesonide. Because there was no direct evidence for targeted-release budesonide compared with systemic corticosteroids and other immunosuppressant therapy, the company did an indirect treatment comparison (ITC) which was provided at technical engagement. The EAG considered that the company had not provided sufficient details on how trials were identified, so it was difficult to know whether all relevant studies were included in the ITC. The committee recalled that systemic corticosteroids are infrequently used for IgAN but agreed that it would consider the results of the ITC. The committee was also aware that the different side effects of targeted-release budesonide and systemic corticosteroids would be important to consider, but that these were not presented as part of the company's ITC. The committee agreed that the results of the ITC were suitable for decision making. The committee concluded that the results suggested that, for both UPCR and eGFR, targeted-release budesonide may be superior to prednisolone and other immunosuppressant therapies, but these results were uncertain.

Economic model

Company's modelling approach

3.10 The company developed a health economic model to assess the cost effectiveness of targeted-release budesonide plus standard care compared with standard care alone for people with IgAN. The model used a cohort-level state transition approach with 6 health states defined according to 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 states from NefIgArd Nef-301 part A. The EAG considered the company's overall model structure to be reasonable, but had concerns about the validity of the assumption that allowed people in CKD health states 1 to 4 to transition to improved neighbouring health states. The company responded that this assumption was validated with clinical experts and that the model structure was aligned with that used in NICE's technology appraisal guidance on dapagliflozin for treating chronic kidney disease (TA775). 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 in the placebo plus standard care arm was informed using real-world evidence from people with IgAN and a UPCR of 1.5 g/g or more from the UK RaDaR database. The EAG confirmed that this was a reasonable approach. In addition to the model structure, the committee was aware that the company's assumptions for health state utilities and health state costs were also aligned with the economic model in TA775. The EAG confirmed that this was a reasonable approach. The committee concluded that the company's model structure was appropriate.

Assumptions about retreatment

3.11 The course of treatment with targeted-release budesonide is 9 months. The marketing authorisation states that retreatment may be considered at the discretion of the treating physician, but the safety and efficacy of retreatment with targeted-release budesonide has not been established. The company consulted with 2 clinical experts at technical engagement to gain advice on the number and effectiveness of subsequent rounds of treatment, and the

percentage of people who would be expected to have them:

- For the number of rounds of treatment, the company's 2 clinical experts agreed that people with IgAN would have about 2 rounds of treatment, provided an acceptable level of tolerability is maintained. The clinical experts present at the NICE evaluation committee meeting confirmed that multiple rounds of retreatment would likely be needed and that the population with IgAN tends to be quite young compared with other types of CKD. They further noted that because it is a very heterogenous population, retreatment would likely be considered on a case-by-case basis considering the risk to benefit profile for the individual, as is done with other corticosteroids.
- For the proportion of people who would have retreatment, the company stated that its 2 clinical experts estimated that either 50% or 100% of people who finished their initial treatment course of targeted-release budesonide and were still classified as having CKD stages 1 to 3b would be expected to have retreatment within their lifetime. For its updated model the company opted to use 75%, the midpoint between these 2 estimates. The company further noted that the model assumed that people whose IgAN had not had a response to the initial treatment would not have retreatment with targeted-release budesonide.
- For treatment effectiveness, the company applied 90% of the treatment effect from the first course of targeted-release budesonide. The company explained that this was not based on clinical expert advice, but was selected as a conservative value, considering that there is some clinical uncertainty. The clinical experts present at the NICE evaluation committee meeting explained that there is no evidence to suggest that targeted-release budesonide would be less effective in subsequent rounds of treatment. This is because other corticosteroids are used repeatedly over many years for a variety of different conditions (for example, asthma) and it is not thought that such treatments become less effective through repeated use.

  The EAG agreed with the company that its retreatment assumptions after technical engagement were appropriate for use in the economic model but noted that there was remaining uncertainty around them. The committee considered all scenario analyses from the company and EAG exploring the different retreatment assumptions. The committee expressed concerns about

the potential for increased adverse effects with more rounds of treatment. It noted that it had not been presented with any evidence on retreatment clinical effectiveness or the adverse effects associated with repeated dosing because there is no available data, although it noted a trial assessing repeated dosing was ongoing. On the question of the cost impact of allowing for more rounds of retreatment, the EAG stated that in the model additional rounds of treatment meant that targeted-release budesonide becomes more cost saving. This was because people remained in the lower CKD health states for longer, so avoided progressing to higher CKD health states that are associated with much higher treatment costs because of the increasing frequency of dialysis and kidney transplants. The committee noted that there was only evidence from the clinical trial for 1 round of treatment with targeted-release budesonide. It agreed that it would consider the cost effectiveness of 1 round of treatment and also the impact of scenarios exploring repeated rounds of retreatment in its decision making. The committee concluded that there is uncertainty around the health benefits and cost effectiveness of repeated rounds of retreatment, and noted its concerns about possible increased risk of adverse effects. But it further concluded that additional rounds of retreatment appear to improve the cost effectiveness of targeted-release budesonide.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.12 The committee considered the cost effectiveness of targeted-release budesonide plus standard care compared with standard care alone in people with a baseline UPCR of 1.5 g/g or more. In the company's updated model, the incremental cost-effectiveness ratio (ICER) for targeted-release budesonide plus standard care compared with standard care was £4,672 per quality adjusted life year (QALY) gained. The EAG did not present separate exploratory base-case results because it agreed with the company's revised assumptions after technical engagement. The committee noted that the EAG had corrected some errors in the company's probabilistic model after technical engagement, which the company accepted. The probabilistic ICER was £7,916 per QALY gained. The

committee noted that the deterministic ICER assuming no retreatment was £10,564 per QALY gained, and 3 or more rounds of retreatment resulted in targeted-release budesonide with standard care being less costly and more effective than standard care alone. The committee noted that using data from more people in part B of NefIgArd Nef-301 in the model also resulted in targeted-release budesonide with standard care being less costly and more effective than standard care alone. It recognised that standard care in the company model did not include systemic corticosteroids. An exploratory analysis based on the ITC estimated an ICER of £25,000 per QALY gained for targeted-release budesonide compared with prednisolone. But this estimate was highly uncertain because of the limitations of the data. Overall, for the small proportion of people who would have systemic corticosteroids, the committee considered that targeted-release budesonide would be expected to be as clinically effective but probably with fewer side effects. The committee concluded that the most likely cost-effectiveness estimate for targeted-release budesonide compared with standard care, including systemic corticosteroids for a small proportion of the population, 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

3.13 The committee considered that there were no equality issues.

Conclusion

Recommendation

3.14 The committee was satisfied 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 considered that there was limited data currently available on repeated use of targeted-release budesonide,

but having repeated treatment was unlikely to make it cost-ineffective in clinical practice. The committee also noted the uncertainty of not including prednisolone in the modelled standard care arm for a small proportion of people. So targeted-release budesonide is recommended as an add-on to standard care with maximally tolerated RASi therapy for treating primary IgAN when there is a risk of rapid disease progression in adults with a UPCR of 1.5 g/g or more.

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 3 months 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 2 months 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 doctor 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

This topic was evaluated as a single technology appraisal by the highly specialised technologies evaluation committee. Because of this, some members of the technology appraisal committees were brought in to provide additional expertise to the committee. The 4 technology appraisal committees and the highly specialised technologies evaluation committee are standing advisory committees of NICE.

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

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

Chair

Peter Jackson
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 and a project manager.

Luke Cowie
Technical lead

Mary Hughes
Technical adviser

Celia Mayers
Project manager

6 Update information

October 2025: We updated recommendation 1.1 to change the unit for urine protein-to-creatinine ratio (UPCR) to mg/mmol from g/g. A UPCR of 170 mg/mmol or more equates to the 1.5 g/g or more measurement specified in the marketing authorisation indication for targeted-release budesonide.

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