NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Obinutuzumab with mycophenolate mofetil for treating lupus nephritis

1 Recommendation

1.1 Obinutuzumab plus mycophenolate mofetil can be used, within its marketing authorisation, as an option to treat active class 3 or 4 (with or without class 5) lupus nephritis in adults. It can only be used if the company provides obinutuzumab according to the commercial arrangement (see section 2).

What this means in practice

Obinutuzumab plus mycophenolate mofetil must be funded in the NHS in England for the condition and population in the recommendation, if it is considered the most suitable treatment option. It must be funded in England within 90 days of final publication of this guidance.

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

Why the committee made this recommendation

Usual treatment for lupus nephritis includes mycophenolate mofetil alone or mycophenolate mofetil plus belimumab, rituximab or voclosporin (all given with corticosteroids).

Clinical trial evidence shows that obinutuzumab plus mycophenolate mofetil increases the chance of complete renal response and increases the time to renal flare compared with mycophenolate mofetil alone. Obinutuzumab plus mycophenolate mofetil has not been directly compared in a clinical trial with belimumab, rituximab or voclosporin. But indirect comparisons suggest it is likely to work as well as these.

The cost-effectiveness estimates that reflect the treatment comparisons most likely in clinical practice are within the range that NICE considers an acceptable use of NHS resources. So, obinutuzumab can be used.

2 Information about obinutuzumab

Marketing authorisation indication

2.1 Obinutuzumab (Gazyvaro, Roche), in combination with mycophenolate mofetil (MMF) is indicated for 'the treatment of adult patients with active Class III or IV, with or without concomitant Class V, lupus nephritis (LN)'.

Dosage in the marketing authorisation

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

Price

2.3 The list price is £3,312.00 per 1,000-mg vial (excluding VAT, BNF online, accessed December 2025).

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

Sustainability

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on Roche's website.

3 Committee discussion

The evaluation committee considered evidence submitted by Roche, 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 condition

3.1 Lupus nephritis is a complication of systemic lupus erythematosus. About 60% of people with systemic lupus erythematosus develop lupus nephritis. The body's immune system targets kidney cells, particularly the filtering units called glomeruli. This causes inflammation (nephritis). Symptoms include fatigue, blood or foam in urine, swollen legs and high blood pressure. The patient expert explained that lupus nephritis is a relapsing-remitting condition. During relapses, the kidneys become particularly inflamed (known as renal flares). The clinical experts explained that renal flares can cause permanent damage by scarring the kidney, which leads to reductions in kidney function and progression towards end-stage renal disease. The patient expert explained that lupus nephritis affects many aspects of life, reducing quality of life. They explained that reaching remission is key for people with lupus nephritis. The clinical experts advised that the current treatment options are insufficient for inducing remission and they would welcome a new treatment option for lupus nephritis. The committee concluded that lupus nephritis is a debilitating condition and there is a need for effective treatments that achieve stable and long-term remission.

Comparators

Treatment options

3.2 First treatment for lupus nephritis includes mycophenolate mofetil (MMF) plus corticosteroids (referred to as MMF alone from now). If MMF alone is insufficient to induce remission, another treatment is added. But the clinical experts advised that triple therapy (MMF, corticosteroids and a third treatment) is becoming more common as a starting treatment. So, MMF alone is not a common treatment in clinical practice. Options for the third treatment include rituximab, belimumab and voclosporin. The clinical experts advised that most people would have rituximab, with fewer people having belimumab or voclosporin. They noted that MMF and voclosporin are both oral treatments and the pill burden for lupus nephritis is very high, which the patient expert agreed with. But obinutuzumab is an intravenous treatment, which would reduce the pill burden and require less frequent administration than rituximab or belimumab. The clinical experts advised that rituximab is used off-label and there is limited randomised controlled trial evidence on its effectiveness for lupus nephritis. So, the clinical experts rely on their clinical experience when deciding if rituximab is a suitable treatment option. The committee acknowledged that obinutuzumab would be used as another option in combination with MMF. It concluded that the comparators are suitable, with rituximab being the main comparator.

Clinical effectiveness

Data sources

3.3 Clinical evidence came from an ongoing, international, phase 3, double-blind randomised trial (REGENCY) with supporting evidence from a phase-2 trial (NOBILITY). REGENCY compared the efficacy of obinutuzumab plus MMF with MMF alone in people with class 3 or 4, with or without class 5, lupus nephritis. The primary endpoint of REGENCY was assessed at 76 weeks. The EAG was concerned that this period may

not be long enough to capture relapse rates for obinutuzumab, noting that some people may have treatment for more than 10 years. The clinical experts noted the relapsing and remitting nature of lupus nephritis and said that 76 weeks was a reasonable duration to capture relevant differences in relapse rates. The primary outcome of REGENCY was difference in proportion of complete renal response (CRR). 46.4% of people in the obinutuzumab arm had CRR at week 76 compared with 33.1% in the MMF-alone arm, which was a statistically significant difference (p=0.0232). Another key outcome for the model was time to renal flare. People in the obinutuzumab arm had a statistically significantly longer time to renal flare compared with MMF alone (hazard ratio 0.44, 95% confidence interval 0.24 to 0.82, p=0.0074). The clinical experts advised that proteinuria was an important outcome, linked to levels of inflammation and long-term kidney outcomes. 55.5% of people in the obinutuzumab arm had proteinuric response in REGENCY at week 76 compared with 41.9% in the placebo arm, which was statistically significant (p=0.0227). The committee acknowledged the significant results in the key outcomes. It concluded that evidence from REGENCY was suitable for decision making.

Indirect treatment analysis

3.4 The company did a network meta-analysis including rituximab, belimumab and voclosporin. The network was connected through the MMF-alone arms in 6 trials of MMF plus:

- obinutuzumab (REGENCY and NOBILITY)
- rituximab (LUNAR)
- belimumab (BLISS-LN)
- voclosporin (AURA-LV and AURORA-1).

The company noted that CRR had different definitions across the trials and recommended cautious interpretation of the results. The EAG also

noted the differences in outcome definitions between trials, also noting differences in the populations of the trials. It was concerned that the differences between the trials may violate the transitivity assumption required for network meta-analyses. This is the assumption of sufficient clinical and methodological similarity (homogeneity) between the included studies, across all comparisons. The EAG also noted that there were no statistically significant differences between obinutuzumab plus MMF and any other comparators for the CRR outcome (the exact results are considered confidential by the company and cannot be reported here). The committee acknowledged that the results of the network meta-analysis were uncertain but concluded that they could be used for decision making.

Economic model

Company's modelling approach

3.5 The company used a nine-state Markov model based on the model used in NICE's technology appraisal guidance on voclosporin with mycophenolate mofetil for treating lupus nephritis [TA882] to estimate the cost-effectiveness of obinutuzumab plus MMF. The model was separated into 3 groups: chronic kidney disease (CKD) stage 1 to 3b, CKD stage 4 and CKD stage 5. The CKD stage 1 to 3b and CKD stage 4 groups had health states for complete response, partial response and active disease. The CKD stage 5 group had health states for dialysis and kidney transplant. The model used a cycle length of 6 months. The committee noted that in the model used in TA882 the first group was CKD stage 1 to 3a, and the second group was CKD stage 3b to 4. The company said its health state definitions were slightly different because the inclusion criteria for REGENCY included people with stage 3b CKD. But AURORA-1 (the key trial used to inform the cost-effectiveness model in TA882) only included people up to CKD stage 3a. The committee concluded that the model was suitable for decision making.

Time to renal flare as a proxy

3.6 The company used time to renal flare as a proxy for predicting the probability of transitioning to CKD stage 4 in the economic model. It used results from a Bucher indirect treatment comparison (ITC), separate to its main network meta-analysis (see section 3.4), comparing results from REGENCY, AURORA-2 and BLISS-LN to derive the hazard ratio of renal flare for obinutuzumab, voclosporin and belimumab. In the company's base case, the base transition probability from stage 1 to 3b CKD to stage 4 was 3.05% per cycle with MMF alone. For obinutuzumab, voclosporin and belimumab the probability was adjusted down based on the hazard ratios for time to renal flare compared with MMF alone from the respective trials. The company noted evidence from a published study by Perez Arias et al. 2023 that renal flares worsen kidney outcomes and long-term prognosis. But it acknowledged the uncertainty in assuming time to renal flare as a proxy for predicting the probability of transitioning to CKD stage 4. So, it did scenario analyses that adjusted the strength of the hazard ratio adjustment between 100% and 0%. The EAG noted that the evidence provided by the company did not show a link between time to renal flare and CKD progression. Instead, it showed a link between repeated renal flares and CKD progression. The EAG was concerned about the company's use of a Bucher ITC to estimate the hazard ratios. This is because of the lack of adjustment for differences in patient characteristics across the trials and limited reporting of methods in the company's submission. The EAG noted that the model already accounted for improvements in renal response reducing progression and that including additional adjustment based on time to renal flare may double-count the effectiveness of treatments on CKD progression. So, it removed the adjustment to the probability of transitioning to CKD stage 4 based on time to renal flare in its base case. The clinical experts advised that there was a strong link between CKD progression and number of renal flares, and that the link with time to renal flare was unclear but likely to be

present. They noted that consideration of a wider range of biomarkers for disease activity would ideally be required to predict CKD progression. The company agreed that time to renal flare was not the most ideal outcome to use for adjusting progression, but it was the best available outcome from the trial. The committee acknowledged there likely was a link between time to renal flare and CKD progression, but it was unable to quantify this. It noted the EAG's concern that including the adjustment may lead to double-counting the effectiveness of obinutuzumab. It noted that this assumption was likely conservative but decided it was reasonable considering the lack of evidence around time to renal flare as a proxy for progression. So, the committee concluded that the EAG's base case was uncertain but was the most suitable for decision-making.

Outcome endpoints in the model

3.7 The company used results from REGENCY and the network meta-analysis to calculate the rates of CRR and partial renal response (PRR) of each treatment in the model. The longest follow-up timepoint across the trials included in the company's network meta-analysis was 2 years. To do the network meta-analysis, the company said it needed to use a common follow-up time to extrapolate the trial endpoints out to. It used a timepoint of 3 years to align with the expected duration of most treatments in clinical practice. The company noted that its choice of a 3-year endpoint assumed the results at the end of each trial would be the same at 3 years, which it acknowledged was a strong assumption. The EAG agreed that unless the probability of reaching CRR and PRR were unlikely to change between week 76 (1.5 years) and week 157 (3 years) of treatment, the approach used by the company was likely to be inappropriate. It preferred to use a 1.5-year endpoint to better align with the follow-up timepoint in REGENCY. The company used a Weibull distribution to transform the probabilities to reflect the 6-month cycle length in the model. The EAG instead used the exponential function to transform probabilities to the 6-month cycle length in the model, citing Gidwani and Russell (2020). The

clinical experts explained that the biomarkers for kidney disease are imperfect for measuring response. They advised that response to treatment could take up to 2 years. The committee noted that evidence was limited to support the company's assumption of constant response rates between 1.5 and 3 years. The committee concluded that the EAG's base case was most suitable for decision-making because it aligned most closely with the follow-up timepoint of the key trial evidence.

Treatment-effect waning

3.8 The company used a 3-year stopping rule for all treatments in the model. After the stopping rule, different treatment-effect waning assumptions were applied to each treatment. The full effect of treatment was maintained for 12 months beyond stopping treatment for obinutuzumab and for 6 months beyond stopping treatment for rituximab and belimumab. After the full treatment effect finished, the treatment effect was assumed to wane to that of MMF alone over a period of 12 months for obinutuzumab and over 6 months for rituximab, belimumab and voclosporin. The company said that response to obinutuzumab was largely influenced by the level of B-cell depletion, noting that evidence from REGENCY and NOBILITY suggested that B-cell depletion was maintained over a long period after treatment with obinutuzumab. It said that clinical experts had advised that rituximab was not as proficient at maintaining B-cell depletion as obinutuzumab. It assumed that belimumab had the same treatment-effect waning as rituximab. The EAG said that there was no evidence of maintaining treatment effect after the 3-year stopping rule, and that the company's assumptions mainly relied on clinical expert opinion. It preferred to keep the company's maintenance periods of full treatment effect in its base case but remove the waning assumptions beyond this because of lack of longer-term evidence. The clinical experts agreed that obinutuzumab would have the longest duration of B-cell depletion of the included treatments. They expect that there would be some maintenance of full treatment effect beyond stopping

treatment, and some treatment-effect waning. But they advised that the company's base case likely overestimated the duration of these effects, particularly for rituximab and belimumab, which they expect to have a maximum maintenance of full treatment effect beyond stopping treatment of about 3 months each. The clinical experts also said that duration of treatment varied in clinical practice but would aim to continue for at least 3 years and potentially up to 5 years, in line with clinical guidelines. The committee noted that neither the company's nor the EAG's base case matched the clinical experts' opinions. It acknowledged that applying the 3-year stopping rule across all treatments increased the uncertainty in the model results. But it noted that the treatment-effect assumptions in the EAG's base case more closely matched the clinical experts' opinions. So, the committee concluded that the EAG's base case approach to treatment-effect waning was most suitable for decision-making.

Utility values

Source of utility values

3.9 The company used the health state utility values informing decision making in TA882. The company chose these values because the values generated from REGENCY were counterintuitive, with more severe disease states having higher utility (the exact values are considered confidential by the company so cannot be reported here). The EAG agreed that the utility values generated from REGENCY lacked face validity and that the company's approach is appropriate. The committee was concerned that the utility values generated from REGENCY showed no statistically significant difference between the different levels of response. It noted NICE's preference for using utility values from the relevant clinical trial when available. It was concerned that the company had not used the results from REGENCY and instead had used the more favourable results from a previous appraisal. It would have preferred to have seen results using utility values from REGENCY, with adjustments to

address any implausible values. The committee acknowledged the added uncertainty. But it concluded that the TA882 utility values could be used for decision making.

Costs of rescue therapy

3.10 The company used a higher percentage of people having rescue therapy in the MMF-alone arm in the model than was reported in REGENCY (the exact percentages are considered confidential by the company so cannot be reported here). The company said this was because some patients had more than 1 subsequent therapy. The EAG preferred to use the percentage reported in REGENCY, to better align with the reported trial data. The committee noted that the percentage of people having rescue therapy was similar in the company's and EAG's models, and the impact on the cost-effectiveness estimates was small. It agreed that it was reasonable to align the model inputs with the trial data. So, the committee concluded that it preferred the EAG's base-case approach for decision making.

Modelling of other treatments and adverse events

3.11 The EAG's base case differed from the company's base case by changing the frequency of corticosteroid plus MMF administration by treatment arm. It also applied adverse-event disutilities by treatment arm over the entire duration of treatment rather than applying a pooled value to health state utility values in the first cycle of the model. At the committee meeting, the company agreed with the EAG's approach to modelling other treatments and adverse events. The committee concluded the EAG's approaches were acceptable for decision making.

Cost-effectiveness estimates

Acceptable ICER

3.12 NICE's manual on health technology evaluations notes that, above a most plausible 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 incremental cost-effectiveness ratio (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, including:

- the comparability of the trials in the network meta-analysis (see section 3.4)
- the link between time to renal flare and CKD progression (see section 3.6)
- the length of full treatment effect maintained after stopping treatment, waning treatment effect, and the inclusion of the 3-year stopping rule (see section 3.8)
- the lack of face validity in the utility data collected in REGENCY, and the use of utility values in the model that were not from the most relevant trial (see section 3.9).

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

Committee's preferred assumptions

3.13 The committee's preferred assumptions for the cost-effectiveness analysis were:

- not including the adjustment to CKD stage 4 transition probability based on risk of time to renal flare (see section 3.6)
- using an outcome endpoint of 1.5 years for CRR and PRR in the model, transformed using the exponential function (see section 3.7)
- using the EAG's base case for treatment-effect waning assumptions (see section 3.8)

- using the percentage of people needing rescue therapy in the MMF-alone arm of the model from REGENCY (see section 3.10).

These assumptions aligned with the EAG's base case. For the probabilistic analysis comparisons with rituximab and belimumab, obinutuzumab was dominant (obinutuzumab was less costly and more effective). These comparisons used the midpoint of the Medicines Procurement and Supply Chain prices for rituximab. Compared with voclosporin, obinutuzumab was associated with lower costs and slightly lower QALYs. Overall, that meant obinutuzumab was considered a cost-effective use of resources compared with voclosporin. The exact ICERs cannot be reported here because they include confidential discounts for treatments included in the analysis. Compared with MMF alone, the results were slightly above the committee's acceptable ICER of around £20,000 per QALY gained. But the committee noted the clinical experts' opinion that MMF alone is rarely used in clinical practice. So, it concluded that on balance obinutuzumab plus MMF can be considered a cost-effective use of NHS resources.

Other factors

Equality

3.14 The committee noted that lupus nephritis has a higher prevalence in women and people from Asian, Black African or Black Caribbean groups. Active lupus nephritis is also linked with worse outcomes in pregnancy. Sex, race and pregnancy status are protected under the Equality Act 2010. But because the committee's recommendation does not restrict access to treatment for some people over others, this is not a potential equalities issue.

Uncaptured benefits

3.15 The committee considered whether there were any uncaptured benefits of obinutuzumab. It noted that obinutuzumab, as an intravenous treatment, would reduce the high pill burden on people with lupus nephritis. But treatment with obinutuzumab would require travel to specialist treatment centres, which could be burdensome for some people. The committee considered these factors in its decision making.

Conclusion

Recommendation

3.16 The cost-effectiveness estimates for obinutuzumab compared with rituximab, belimumab or voclosporin are within what the committee considered a cost-effective use of NHS resources. The cost-effectiveness estimate compared with MMF alone was slightly above what the committee considered a cost-effective use of NHS resources (see section 3.13). But MMF alone is rarely used in clinical practice and rituximab is the main comparator in this appraisal. So, obinutuzumab plus MMF can be used as an option to treat active class 3 or 4, with or without class 5, lupus nephritis in adults.

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 active class 3 or 4, with or without class 5, lupus nephritis and the healthcare professional responsible for their care thinks that obinutuzumab 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 D.

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

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

Chair

Raju Reddy

Vice chair, technology appraisal committee D

NICE project team

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

George Millington
Technical lead

Rachel Williams
Technical adviser

Kate Moore
Project manager

Ross Dent
Associate director

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