NICE National Institute for Health and Care Excellence

NICE guidance

Belimumab for treating active autoantibody-positive systemic lupus erythematosus

Technology appraisal guidance
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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.

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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

This guidance replaces TA397.

1 Recommendations

1.1 Belimumab is recommended as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus in people with high disease activity despite standard treatment, only if:

- high disease activity is defined as at least 1 serological biomarker (positive anti-double-stranded DNA or low complement) and a SELENA-SLEDAI score of greater than or equal to 10
- treatment is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more
- the company provides belimumab according to the commercial arrangement.

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the managed access agreement for belimumab for systemic lupus erythematosus (NICE technology appraisal guidance 397).

Standard therapies include non-steroidal anti-inflammatory drugs, corticosteroids, antimalarials and immunosuppressants. Other treatments include biological disease-modifying antirheumatic drugs such as rituximab.

Clinical trial evidence suggests that, after a year of treatment, belimumab plus standard therapy reduces disease activity more than standard therapy alone. However, the results are uncertain because the trials were short, so the long-term benefit is unknown. Also, the effect of belimumab compared with rituximab is unknown.

The cost-effectiveness estimates are also uncertain. But there is an unmet need for effective treatments in people with systemic lupus erythematosus, and some benefits of belimumab may not be taken into account in the cost-effectiveness results. For people with high disease activity despite standard treatment, the most likely cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources.

So, belimumab is recommended for these people.

2 Information about belimumab

Marketing authorisation indication

2.1 The intravenous formulation of belimumab (Benlysta, GlaxoSmithKline) 'is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy'. The subcutaneous formulation 'is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedules are available in the summary of product characteristics for the intravenous formulation of belimumab and the summary of product characteristics for the subcutaneous formulation of belimumab.

Price

2.3 The list price of belimumab for the intravenous infusion is £121.50 for a 120-mg vial and £405.00 for a 400-mg vial (excluding VAT; BNF online accessed November 2021). The list price for the subcutaneous injection is £222.75 for a 200-mg pre-filled pen (excluding VAT; company submission).

2.4 The company has a commercial arrangement for both formulations. This makes belimumab 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 appraisal committee considered evidence submitted by GlaxoSmithKline, a review of this submission by the evidence review group (ERG) and responses from stakeholders. See the committee papers for full details of the evidence.

This review looks at data collected using the British Isles Lupus Assessment Group Biologics Register (BILAG-BR) and additional clinical trial evidence presented in the company's updated submission to address uncertainties identified during the original appraisal. As a condition of the managed access arrangement, the company was required to collect real-world data from the BILAG registry after treatment with belimumab, including on its efficacy, safety and effect on health-related quality of life.

The committee agreed that some of the issues raised in the ERG report had been resolved after technical engagement. These included that there is no evidence for using belimumab in people with severe active central nervous system lupus (key issue 1), that cyclophosphamide is not a relevant comparator (key issue 2), and that intravenous and subcutaneous formulations of belimumab are likely to be clinically comparable (key issue 7).

The committee agreed that there is unresolved uncertainty with the issues raised in the ERG report about the uncertainty on organ damage utility multipliers (key issue 12) and the sampling order of organ damage and death in the model (key issue 13). However, it thought that it was unlikely that these issues would have a significant effect on the cost-effectiveness results.

Belimumab as a treatment option

People with systemic lupus erythematous would welcome belimumab as a continuing treatment option

3.1 Systemic lupus erythematosus is a chronic autoimmune condition that causes inflammation in the body's tissues and can affect the whole body. The patient experts explained that people with the condition often have frequent disease flares and more severe symptoms that can result in

hospital admissions. This can affect a person's ability to work, complete everyday activities and socialise. The patient experts described how this causes stress and anxiety, which can trigger further disease flares. They described how the condition can affect fertility by causing recurrent miscarriages and severe disease flares. The patient experts further explained that, even when their condition is clinically stable, they still have symptoms that affect their daily life such as fatigue, headaches, joint pain and reduced mental acuity. These symptoms can make it challenging to care for themselves and others. One patient expert explained that treatment with belimumab as an add-on to standard therapy has significantly reduced their disease flares and that they have been able to reduce their daily corticosteroid dose. The patient experts explained that treatment with belimumab has helped to improve other day-to-day symptoms of the condition, and this has improved their overall quality of life. They described the burden of having to travel long distances to have belimumab intravenous infusions administered in hospital, and that they have nausea from the pre-infusion medication. However, they continue with the treatment because they think that their condition is responding well to it. One patient expert also described the benefits of using the new subcutaneous formulation of belimumab because of being able to self-administer it at home with little disruption to daily life and the minimal side effects. At the second committee meeting, the patient expert explained that they had tried several other treatment options including azathioprine, mycophenolate mofetil and rituximab, but that none of these treatments had effectively reduced their disease activity. They explained that there are few treatment options currently available for people with systemic lupus erythematosus and that they would have no alternative treatment option if belimumab was not made available through routine NHS commissioning. The patient expert explained that the prospect of belimumab being withdrawn was a significant worry for them and many other people with severe refractory disease that has only responded to belimumab. The committee concluded that people with systemic lupus erythematosus would welcome belimumab continuing to be a treatment option.

Treatment pathway and positioning

The company's updated population is appropriate

3.2 The marketing authorisation for belimumab states that it is indicated for systemic lupus erythematosus that has a high disease activity despite standard therapy. The committee discussed that, in the original appraisal, belimumab was recommended for systemic lupus erythematosus with high disease activity (HDA-1) despite standard therapy. HDA-1 is a Safety of Estrogens in Lupus Erythematosus: National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10, and 2 serological biomarkers (positive anti-double-stranded DNA and low complement). The company and clinical experts explained that, based on the data collected through the BILAG registry, this HDA-1 population was too restrictive in clinical practice. This is because people will often have high levels of disease activity but only 1 of the 2 defined serological biomarkers. So, the company presented a broader high-disease-activity population (HDA-2) as part of its base case. This included people with a SELENA-SLEDAI score of greater than or equal to 10 and only 1 serological biomarker. The clinical experts considered that the company's new high-disease-activity population was clinically relevant and would allow more people access to belimumab. The committee concluded that the company's updated population was appropriate for decision making.

Comparators

Standard therapy is a relevant comparator

3.3 The committee heard that standard therapy for treating systemic lupus erythematosus is likely to consist of non-steroidal anti-inflammatory drugs, corticosteroids, antimalarials and immunosuppressants. It was aware that some standard therapies are not licensed for use in systemic lupus erythematosus but are used off label in clinical practice. The committee noted that belimumab is indicated as an add-on therapy to standard care. It understood that standard therapy was included in the

scope for the appraisal and concluded that it was a relevant comparator.

Rituximab is a relevant comparator

3.4 The committee discussed the updated NHS England clinical commissioning policy on rituximab for refractory systemic lupus erythematosus in adults and post-pubescent children. It noted that, while rituximab is currently not licensed for treating systemic lupus erythematosus, it is available as a treatment option through this commissioning policy. The committee discussed the eligibility criteria for rituximab outlined in the commissioning policy, which recommends considering using licensed and NICE-approved treatments, such as belimumab, first. The clinical experts explained that, based on the data collected from the BILAG registry, only a very small number of people on rituximab would be eligible for belimumab because of the differences in the eligibility criteria. They explained that people having belimumab will generally have more severe disease because of the current eligibility criterion of a SELENA-SLEDAI score of greater than or equal to 10. However, they pointed out that people with renal or central nervous system complications would not be eligible for belimumab and would have rituximab instead. The clinical experts also explained that some people who are eligible for belimumab may have experienced adverse reactions or no improvement in their disease activity after treatment with rituximab. Therefore, this population would not be eligible for rituximab. The committee heard that, if belimumab is not recommended for routine commissioning, more people would potentially have treatment with rituximab in its absence. The committee noted that rituximab was included in the final scope for the appraisal and is being used in clinical practice through the commissioning policy. It concluded that rituximab was a relevant comparator.

Clinical effectiveness

Belimumab improves the SRI-4 response rate at 52 weeks compared with standard therapy

3.5 The company submission included the BLISS 52 and BLISS 76

randomised controlled trials comparing intravenous belimumab plus standard therapy (from now, referred to as belimumab) with placebo plus standard therapy (from now, referred to as standard therapy). The company presented results for the new HDA-2 population based on the pooled trials and new evidence from the BLISS SC randomised controlled trial comparing a new subcutaneous formulation of belimumab with standard therapy. The primary outcome of all studies was the response rate at week 52 compared with baseline. This was assessed with the Systemic Lupus Erythematosus Responder Index-4 (SRI-4), which is a composite measure of disease activity. Belimumab showed a statistically significant improvement in SRI-4 response rate at 52 weeks compared with standard therapy in the HDA-2 population across the BLISS SC, and pooled BLISS 52 and BLISS 76 trials (pooled BLISS 52 and BLISS 76: odds ratio 2.29, 95% confidence interval [CI] 1.61 to 3.26; BLISS SC: odds ratio 1.79, 95% CI 1.17 to 2.74). The committee concluded that belimumab improved SRI-4 response rate at 52 weeks compared with standard therapy.

The BLISS long-term extension studies do not provide long-term effectiveness evidence for belimumab compared with standard therapy

3.6 The company included new evidence from the BLISS long-term extension studies. These were single-arm continuation studies of people enrolled in the BLISS randomised controlled trials (see section 3.5). People who had been randomised to have belimumab continued treatment with belimumab, and people in the placebo groups were switched to belimumab in all long-term extension studies:

- The BLISS 76 US long-term extension study included people in the US who had completed the BLISS 76 trial. The primary outcome was mean Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) change from baseline, which is a measure of organ damage. In the total population, the mean SDI change was 0.4 (standard deviation 0.68) at 7 years.
- The BLISS 52/76 non-US long-term extension study included people not from the US who had completed either the BLISS 52 or BLISS 76 trials. In the total

population, the mean SDI change was 0.2 (standard deviation 0.56) at 8 years.

- The BLISS SC long-term extension study included people who had completed the BLISS SC trial. The number of people whose condition responded according to the SRI-4 at 6 months was 16.1% in the placebo-to-belimumab group and 76.3% in the belimumab group.

  The committee noted that the long-term extension studies did not have comparator arms. It concluded that they did not provide long-term effectiveness evidence for belimumab compared with standard therapy.

There is still uncertainty about the clinical and cost effectiveness of belimumab compared with rituximab

3.7 The company explained that no new clinical trial evidence directly comparing belimumab with rituximab had been identified after the original appraisal. It also stated that an indirect comparison based on the EXPLORER trial, which compared rituximab with placebo, was not appropriate. This is because the EXPLORER trial did not meet its primary end point, and for other reasons, such as the trial population including people with more severe disease than people in the BLISS trials. The committee heard that a comparison between belimumab and rituximab was available from the observational prospective cohort BILAG-BR sub-study, which was presented as part of the company's submission. This study was designed to fulfil the managed access requirements from the original appraisal. A multilevel regression analysis done by the University of Manchester compared the efficacy of belimumab with rituximab based on data collected from the sub-study. The eligibility criteria in the study reflected the high disease activity (HDA-1) population recommended in the original appraisal and included people having belimumab, rituximab or other non-biological treatments. Outcome measures assessed in the analysis included measures of disease activity (change in BILAG-2004, SLEDAI-2K and SDI scores), and health-related quality of life measured using generic and disease-specific instruments. The results suggested that, for most outcome measures, a similar level of change in disease activity was seen for belimumab and rituximab at 12 months of follow up (actual results are confidential and cannot be reported here). The company considered that there was a high likelihood of confounding and

selection bias in this regression analysis. It thought that the data was not appropriate for comparing treatment efficacy, so did not do an indirect treatment comparison. The committee noted that the regression analysis based on the observational data did provide a comparison in a UK population relevant to the decision problem. It acknowledged that the analysis was based on small numbers, and the long-term comparative effectiveness between treatments could not be determined based on the 12 months of data collected in the registry for belimumab. The committee considered that because rituximab is a relevant comparator (see section 3.4), it would have preferred to see an indirect treatment comparison between belimumab and rituximab in the relevant population. The company did not provide an indirect comparison between belimumab and rituximab in response to the appraisal consultation document. It considered that as the BILAG-BR sub-study only collected data for the HDA-1 population, an indirect comparison in the target HDA-2 population would not be possible. The company also highlighted that because there is limited long-term effectiveness data for rituximab in people with systemic lupus erythematosus, a reliable and robust indirect treatment comparison cannot be done. The committee recognised that conducting an indirect treatment comparison in the traditional sense may be difficult, but it noted that the company had used an adjusted indirect comparison to compare organ damage progression for people on belimumab and standard care (see section 3.8). It considered that the company could have also explored alternative adjustment methods to inform the treatment comparison between belimumab and rituximab using the data collected from the registry. The committee discussed that because the criteria in the new HDA-2 target population was wider than considered previously, it would still include people who meet the HDA-1 criteria and are currently having belimumab in clinical practice. Therefore, the committee considered that the company should have explored data from the BILAG-BR sub-study to compare efficacy between belimumab and rituximab. It concluded that in the absence of this comparison, the uncertainty about the relative clinical and cost effectiveness of belimumab and rituximab remains.

The results of the propensity score-matched analysis may not be relevant to NHS clinical practice

3.8 The company's long-term extension studies did not have comparator arms. So, it did a propensity score-matched analysis to compare results from people who had belimumab in the BLISS 76 US long-term extension study with the results from people who had standard therapy in the external Toronto Lupus Cohort (n=99 in each cohort). The primary end point of the propensity score-matched analysis was to compare organ damage progression (mean change in SDI score) from baseline to year 5 in people having treatment with belimumab or standard therapy with 5 or more years of follow up. The results showed that people having treatment with belimumab had statistically significantly less organ damage (5-year SDI change of 0.283, 95% CI 0.166 to 0.400) compared with people having standard therapy alone (5-year SDI change of 0.717, 95% CI 0.500 to 0.934). The committee considered that it was unclear why the company had selected the Toronto Lupus Cohort as the source of data for the standard therapy arm in the propensity score-matched analysis. The company explained that it identified the cohort through a systematic literature review of people with systemic lupus erythematosus with 5 or more years of follow up. It selected the Toronto Lupus Cohort because of its size and because it matched on most of the variables needed for the propensity score-matched analysis. The company explained that it did not identify a comparable cohort from the UK through the literature review. The committee considered that it would have preferred data from a UK registry to have been used, but acknowledged the company's comments that such evidence may not be available. The ERG highlighted that it was unclear how selection criteria had been applied to determine that the Toronto Lupus Cohort was the most appropriate source from the systematic review. The committee noted the ERG's critique that the sample size in the BLISS-76 US long-term extension study decreased by almost half in the propensity score-matched analysis, suggesting large differences in the baseline characteristics compared with the Toronto Lupus Cohort. The committee noted a consultation comment that the Toronto Lupus Cohort may not be appropriate for comparison because it included people with systemic lupus erythematosus in a different country, up to 30 years ago. The stakeholder highlighted that changes in medical care since this time may

influence organ damage development and its associated costs. The committee discussed how the 2 cohorts used in the propensity score-matched analysis were from the US and Canada. Because of this, the committee considered that there was uncertainty in the generalisability of the treatment effect observed in the analysis to the target population who would have belimumab in England. The committee concluded that the results of the propensity score-matched analysis may not be relevant to NHS clinical practice.

The results of the propensity score-matched analysis are likely biased in favour of belimumab

3.9 The committee noted that several important variables were not included in the company's propensity score-matched analysis, including measures of socioeconomic outcomes, disease progression and disease activity over time. It discussed the ERG's critique that there were also differences between the populations in the cohorts before matching. These included differences in the rates of smoking, which were higher in the Toronto Lupus Cohort. Because of this, the committee considered that it was likely that people from the Toronto Lupus Cohort would have had worse outcomes, even after matching, because of the influence of these unmatched variables on organ damage progression. In response to consultation, the company explained that it was not suitable to match on variables such as disease progression and disease activity over time because these could be potential confounders in the analysis. The clinical expert agreed that disease activity over time was a potential confounder and that including it could bias the results in either direction. The committee noted the ERG's critique that these variables are important prognostic factors that may need to be adjusted for, to give an unbiased treatment comparison. The committee heard that most people withdrew from the BLISS 76 US long-term extension study before 5 years. So, people who continued having belimumab at 5 years were likely to have progressed less or had a better response than people who had belimumab for 1 to 4 years before stopping treatment. The committee recalled testimony from a patient expert, who described the burden of attending hospital for regular intravenous infusions of belimumab. It agreed that it was likely that people who stayed on belimumab for 5 years had low disease activity, a good response to

treatment or both. The company explained that it had presented the reasons for discontinuation in the BLISS 76 US long-term extension study in its submission. The main reasons for discontinuation were adverse events and patient request. Other reasons for withdrawal included lack of efficacy, physician choice, lack of adherence and loss to follow up. The ERG considered that it was plausible that lack of efficacy would have been a factor in withdrawals stated for other reasons. The clinical experts explained that in clinical trials and clinical practice, people may decide to stop maintenance treatment for reasons other than lack of efficacy, such as their disease being well controlled or in remission, or because they are planning to start a family. They described how systemic lupus erythematosus is a relapsing-remitting disease meaning that a person's disease activity and their resulting need for treatment would vary over time. The committee discussed the ERG's critique that without further data, it is unclear to what extent people who stopped taking belimumab before 5 years were different to those who continued to take belimumab beyond 5 years in the long-term extension study. It discussed that, although some people may have dropped out because they were benefiting, most people would have remained in the trial if they were benefiting from belimumab and those who were not available for analysis at 5 years were likely to have progressed or had a poorer response. The committee concluded that the results of the propensity score-matched analysis were likely biased in favour of belimumab.

Cost effectiveness

The model structure is unchanged from the original appraisal and is suitable for decision making

3.10 The company presented a microsimulation model with an annual cycle length and lifetime time horizon. The model structure was unchanged from the original appraisal. Two separate models were presented for each formulation of belimumab. The models used the new HDA-2 population (see section 3.2), with patient baseline characteristics drawn from the pooled BLISS 52 and BLISS 76 trials for the intravenous belimumab model, and from BLISS SC for the subcutaneous belimumab model. The company used the average patient weight from the BILAG

registry for the intravenous model. In the original appraisal, this was taken from the pooled BLISS 52 and BLISS 76 trials. The committee concluded that, because the model structure remained unchanged from the original appraisal, it was suitable for decision making.

The committee understood why the company had adjusted the model to reflect the observed long-term data available for belimumab

3.11 In the original appraisal, the company simulated long-term effects of belimumab on disease progression using a natural history model based on observational data from a cohort of people with systemic lupus erythematosus (the Johns Hopkins lupus cohort). In this review, the company explained that the newly available BLISS long-term extension studies (BLISS 52 and BLISS 76) were incorporated to extrapolate long-term effects on disease progression. The company considered that, compared with results from the propensity score-matched analysis (see section 3.8), its model overestimated organ damage progression in the belimumab arm but underestimated progression in the standard therapy arm. So, the company simulated its model using several calibration factors until the results matched the observed results from the propensity score-matched analysis at 5 years. The chosen calibration factor (0.491) was then applied to belimumab 'responders' only (see section 3.13) for up to 6 years and was used to adjust the time-to-event risk equations for organ damage probabilities in the models. The ERG noted that this implied that the annual risk of organ damage for belimumab was adjusted downwards by 50.9%. The committee understood why the company had adjusted organ damage progression in the original model to reflect the observed long-term data available for belimumab but had concerns about how this had been done (see section 3.12).

The company's calibration factor to adjust for long-term organ damage is not suitable for decision making

3.12 The ERG noted that the main issue with applying the calibration factor was that the propensity score-matched analysis it was based on had

several methodological issues (see section 3.8 and section 3.9). Another concern was that the model assumptions in the original appraisal assumed a constant treatment effect of belimumab on disease activity reduction after 1 year (based on the trial data). The committee considered that this was already an optimistic assumption in terms of the long-term treatment effect of belimumab. This was particularly so when taking into account that some people stopped treatment in the long-term extension studies (that is, after 1 year) because of a lack of efficacy. The committee also considered that adding the calibration factor would have further increased the treatment benefit of belimumab. It noted the ERG's comments that the company's calibration factor was derived using the entire modelled belimumab cohort (including people whose condition responded and did not respond to belimumab, classified as 'responders' and 'non-responders' respectively – see section 3.13). The ERG noted that the propensity score-matched analysis on which the calibration factor was based only included people who had treatment for 5 years or longer and so would have experienced a good response to treatment. Therefore, it considered that only 'responders' to belimumab should have been used in the model to derive the calibration factor. In response to the ERG's critique, the company provided a scenario analysis using 'responders' only to derive a calibration factor. The scenario analysis resulted in a calibration factor of 0.536, which was slightly less favourable for belimumab than the original calibration factor used in the company's base case. The committee noted that applying the new calibration factor had a small impact on the incremental cost-effectiveness ratio (ICER). It was concerned that the difference between the new and original calibration factor was smaller than expected and that removing 'non-responders' only had a small impact on organ damage progression of the entire modelled belimumab cohort at 5 years. The ERG suggested that this may mean that organ damage of 'non-responders' may be underestimated in the model and that this could bias the derivation of the calibration factor. The clinical experts explained that this small difference could be because 'non-responders' would likely have their standard therapy adjusted and this may improve their disease activity for some time. The committee discussed that because the calibration factor is applied as a multiplication to the model, this means that any associated error and uncertainty is likely to accumulate over time. It recalled its concern about the appropriateness of the propensity

score-matched analysis that formed the basis of the calibration factor. The committee noted the ERG's critique that applying the calibration factor that has been estimated based on 5 years is likely to underestimate organ damage progression in the preceding years. It noted the uncertainty in applying the calibration factor constantly to belimumab 'responders' who stopped treatment at years 2 to 4 in the model. The committee discussed how the ERG was not able to fully validate the company's new calibration factor and that it likely overestimated the treatment benefit of belimumab. The committee concluded that the company's calibration factor to adjust for long-term organ damage was not suitable for decision-making.

It is unclear whether the modelled response to treatment for belimumab 'non-responders' is consistent with the BLISS trials

3.13 In the original appraisal, the committee heard from clinical experts that people would likely stop treatment with belimumab after 24 weeks if they had not experienced any improvement in their disease control during this time (in line with summary of product characteristics for belimumab). The clinical experts indicated in the original appraisal that a SELENA-SLEDAI score reduction of 4 points would generally be considered a reasonable improvement and the committee noted that this was aligned with the 24-week treatment continuation rule in the company's model. In the model, people on belimumab with a reduction of 4 or more points in SELENA-SLEDAI score at week 24 were classified as 'responders'. SELENA-SLEDAI scores were estimated based on a regression model, given that there was not a 24-week time point in the model. The committee noted that, at 24 weeks, 34.1% of people from the HDA-2 subgroup were classified as 'non-responders' using the regression model and stopped treatment with belimumab. The committee did not think it was clinically plausible that nearly half of these modelled 'non-responders' (46.5%) would have had a SELENA-SLEDAI score reduction of 4 or more at 52 weeks after reverting to standard therapy alone at 24 weeks, as predicted by the company's model. The ERG noted that the model could have underestimated belimumab costs compared with clinical practice because people having a response to belimumab at 52 weeks were initially classified as 'non-responders' and therefore modelled to stop treatment with belimumab. The company explained that

this observation did not mean that these people were incorrectly classified in the model as 'non-responders'. It highlighted that no one classed as a belimumab 'non-responder' at 24 weeks had a SELENA-SLEDAI reduction of 4 or more points. The clinical experts explained that standard care for lupus treatments in clinical trials includes a combination of immunosuppressants, hydroxychloroquine and high-dose corticosteroids. Because of this, they considered that it was possible for some people to have a benefit with standard therapies, particularly because regular care in clinical trials is usually better than clinical practice. The clinical experts considered that people whose condition has not responded to belimumab would have their standard therapy adjusted, for example, by dose escalation. This may result in an improvement in disease activity within 3 to 6 months of changing treatments for some people. The committee was not convinced that people whose condition has not responded to belimumab at 24 weeks would have a significant improvement in disease activity at 52 weeks on standard therapy alone. It considered that a 6-month cycle length may have been more appropriate to use in the model to align with the 24-week continuation rule. In response to the appraisal consultation document, the company presented a post hoc analysis of the pooled BLISS 52 and BLISS 76 trial data, which showed that 34.5% of 'non-responders' to belimumab at week 24 became 'responders' at week 52. The ERG considered that compared with the trial data, the company's model overestimated the number of 'non-responders' to belimumab at week 24 who became 'responders' at week 52. The company explained that this was because while 'non-responders' could continue to have belimumab in the BLISS trials, their steroid therapy was not allowed to be adjusted after week 40. However, in the model, 'non-responders' stopped belimumab treatment at 24 weeks and would then have their steroid therapy adjusted to improve disease control to reflect clinical practice. The committee noted the ERG's concern that disease activity in 'non-responders' to belimumab may be underestimated in the model compared with the BLISS trials. The ERG explained that it was unable to validate the extended benefit that 'non-responders' receive in the model after stopping treatment with belimumab. The committee understood that the impact of this on the cost-effectiveness results was unknown. It concluded that it was unclear whether the modelled response to treatment for belimumab 'non-responders' was consistent with the BLISS

trials.

Disease activity should be based on the BLISS trials for the first 52 weeks for people whose condition has not responded to belimumab

3.14 The ERG suggested that there was an error in the company's model because 'non-responders' had the same reduction in disease activity as people having standard therapy at 52 weeks. It considered that this likely meant the treatment benefit of belimumab was overestimated. This is because the BLISS trials showed that people whose condition did not respond to belimumab had a smaller reduction in disease activity than people having standard therapy in the first 52 weeks. The company considered that this was not an error in the model, but an assumption that 'non-responders' took the average standard therapy score from week 52 onwards. The company explained that this assumption was made because 'non-responders' to belimumab at week 24 switched to standard therapy for the remainder of the modelled time horizon (see section 3.13). The ERG explained that, because the model had a yearly cycle, this assumption did not capture any disadvantage that 'non-responders' to belimumab may have in the first 52 weeks, and was not in line with the BLISS trials. The company's scenario analysis assumed a return to standard therapy efficacy for 'non-responders' by week 76 instead of at 52 weeks as in the company's base case. The committee noted that this had a small effect on the ICER. In response to the appraisal consultation document, the company acknowledged the ERG's comments and presented a further scenario analysis. This added an additional cost to belimumab 'non-responders' in year 1 of the model to allow for treatment of their high disease activity. The committee noted that this also had a small effect on the ICER. It discussed the ERG's base case, which used the BLISS evidence to incorporate the difference in disease activity between 'non-responders' and people having standard therapy in the first 52 weeks. The committee preferred the ERG's approach and concluded that disease activity for people whose condition has not responded to belimumab should be based on the BLISS trials for the first 52 weeks.

There is still uncertainty around the effect of the error in utility estimation on the cost-effectiveness results

3.15 The ERG explained that the company's utility regression model used to estimate utility values excluded key organ damage coefficients without re-estimating the remaining coefficients used in the regression equation. The company agreed that this was an error but did not provide a re-estimated model during technical engagement or in response to the appraisal consultation document. Instead, the company presented scenario analyses to explore the effect of varying the regression utility coefficients (log of age, constant, SLEDAI score, ethnicity) in the regression equation by 1 standard deviation in each direction. The committee considered that the company scenarios likely explored the full impact on the cost-effectiveness results but noted that ICERs increased or decreased by around £3,000 per quality-adjusted life year (QALY) gained with only 1 of the coefficients varied. It noted the ERG's critique that the ICERs could increase or decrease further with combinations of coefficients varied but that the variation by 1 standard deviation was likely substantial. The committee considered that it would have preferred the company to provide a re-estimated model to resolve the uncertainty in the cost-effectiveness results. Therefore, the committee concluded that there is still uncertainty around the effect of the error in utility estimation on the cost-effectiveness results.

Cost-effectiveness estimates

The committee would be prepared to accept an ICER greater than £20,000

3.16 NICE's guide to the methods of technology appraisal notes that, above a most plausible ICER of £20,000 per 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. So, the committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee discussed that the ERG's analyses may be slightly pessimistic because they did not adjust for the long-term data available for belimumab. However, it did not

accept the company's base cases because of the issues around the appropriateness of the propensity score-matched analysis and the company's calibration factor. Furthermore, it considered that there was uncertainty about the cost-effectiveness estimates because it was unclear whether the disease activity of 'non-responders' to belimumab had been underestimated in the model and because of the company's error in utility estimation. The committee noted that the clinical evidence presented by the company did not inform a reliable long-term comparison of belimumab with standard therapy, and the company had not presented an indirect comparison or cost-effectiveness results compared with rituximab, which it considered to be a relevant comparator. The committee was willing to be flexible despite these uncertainties, which would otherwise limit what would be an acceptable ICER. It took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and the additional benefits of belimumab that may not be captured in the cost-effectiveness results (see section 3.19). Therefore, it agreed that it would consider ICERs near to the upper end of the range normally considered a cost-effective use of NHS resources.

Belimumab compared with standard therapy is cost effective

3.17 After consultation, the company updated its confidential patient access scheme for belimumab. The company's deterministic base-case ICER (using the updated patient access scheme for belimumab) compared with standard therapy was £12,335 per QALY gained for the intravenous formulation of belimumab and £8,480 per QALY gained for the subcutaneous formulation. The ERG presented analyses including the committee's preferred modelling assumptions, which:

- removed the calibration factor (see section 3.12)
- used the BLISS trial evidence to incorporate the difference in disease activity between people whose condition has not responded to belimumab and people having standard therapy in the first 52 weeks (see section 3.14).

  Using the updated patient access scheme for belimumab, the ERG's deterministic base-case ICERs were £30,278 per QALY gained for the

intravenous formulation of belimumab and £29,313 per QALY gained for the subcutaneous formulation. The committee considered that the most plausible ICERs for belimumab compared with standard therapy would likely fall in between the company's and ERG's base-case deterministic ICERs. Therefore, it considered that both formulations of belimumab would be a cost-effective use of NHS resources.

Other factors

There are no equality issues that can be addressed in this technology appraisal

3.18 The committee understood that systemic lupus erythematosus mainly affects women, particularly those of child-bearing age. The patient experts explained that there is a risk of harm to an unborn baby (if taken during pregnancy) and infertility with most immunosuppressive and biological treatments. This can make family planning challenging. The clinical experts explained that neither rituximab nor belimumab is considered safer than the other for use in pregnancy. However, because belimumab has a short biological half-life and so is administered monthly, this makes it easier to organise a planned conception compared with rituximab which has a much longer-lasting effect. The committee recognised that if belimumab was not recommended, then this could potentially make it more difficult for women of reproductive age to plan a pregnancy. The committee heard how the condition is more common in people from an African, Caribbean and Asian family background and that they tend to have poorer health outcomes than people from other family backgrounds. It noted stakeholder comments that anti-double-stranded-DNA antibodies may be less common in people from certain ethnic groups, and that any recommendation about belimumab use stating this as a criterion could be considered as discriminatory. The committee was aware that the company's updated population meant that only 1 of the 2 biomarkers was needed for someone to be eligible for treatment with belimumab. It also heard that administering intravenous belimumab in a specialist centre may be a barrier to accessing treatment if a person lives far away and has to take time off work to have regular infusions. The committee discussed that having a subcutaneous formulation that can

be self-administered may improve access to belimumab but noted that the subcutaneous formulation is currently not licensed in children. It noted a stakeholder comment that while childhood systemic lupus erythematous is relatively rare, it usually has a more severe presentation than in adults. This may have a significant impact on a child's education and caring requirements for parents. The committee understood that the intravenous formulation of belimumab is currently being used in children aged 5 years and older through the NHS England's Commissioning Medicines for Children in Specialised Services. It noted comments received during consultation that if belimumab was not recommended for routine commissioning, then this may increase inequalities in access to rituximab. This is because rituximab is only available as an intravenous infusion administered at a specialist centre and some people may struggle to access these centres. Furthermore, rituximab is currently not commissioned for use in children who have not started puberty. The committee concluded that issues about differences in prevalence or incidence of a condition and healthcare implementation cannot be addressed in a technology appraisal.

There are additional benefits of belimumab that may not be captured in the cost-effectiveness analysis

3.19 The company considers belimumab as an add-on to standard therapy to be innovative because it reduces disease activity and corticosteroid use in people with systemic lupus erythematosus. The committee agreed that these are important benefits and recognised that belimumab is the only medicine specifically licensed for treating systemic lupus erythematosus. It recalled comments received during consultation and from the patient experts highlighting that there is an unmet need for effective treatments in people with systemic lupus erythematosus, particularly in those with severe refractory disease. The committee recognised that the subcutaneous formulation of belimumab, which can be self-administered at home, can offer benefits over the intravenous formulation. The patient experts explained that the intravenous formulation of belimumab also offers significant benefits compared with rituximab. This includes a shorter infusion time and minimal side effects after the infusion. The clinical experts explained that people with rare autoimmune rheumatic diseases such as systemic lupus erythematosus

are at an increased risk of adverse and serious effects if they contract COVID-19. They explained that there is some evidence that people having treatment with rituximab are likely to have a low or undetectable immune response to COVID-19 vaccinations. This is because rituximab works by depleting a person's B cells, which interferes with the immune system's ability to develop a response to new antigens. The clinical experts explained that because the biological half-life of rituximab is between 6 and 12 months, this means that vaccination efficacy may be significantly reduced if it is given during this time. The committee noted that it had not seen any data on the level of immune response to COVID-19 vaccinations in people having belimumab. The clinical experts confirmed that they were not aware of any such evidence but would expect that because belimumab does not have the same impact on a person's B cells as rituximab and has a much shorter biological half-life, it would likely have a less severe impact on vaccine efficacy. The committee concluded that there are additional benefits of belimumab that may not be captured in the cost-effectiveness analysis.

Conclusion

Belimumab is recommended for routine use

3.20 The committee recognised that people with systemic lupus erythematous have benefitted from treatment with belimumab, and that using the subcutaneous formulation at home has advantages. It acknowledged that belimumab compared with standard therapy improves disease outcomes, but that comparative long-term evidence is lacking. It considered that some of the assumptions used in the modelling were not appropriate and that there was uncertainty about the cost-effectiveness estimates. The committee noted that rituximab was a relevant comparator but that the company had not presented any indirect comparison or cost-effectiveness results for belimumab compared with rituximab. However, it took into consideration the unmet need for effective treatments in people with systemic lupus erythematosus and that there are benefits of belimumab that may not be captured in the cost-effectiveness results. The committee considered that the most plausible ICERs using its preferred modelling assumptions

were within the range that NICE normally considers to be a cost-effective use of NHS resources. So, it recommended belimumab for treating active autoantibody-positive systemic lupus erythematosus.

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 clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal 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 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 appraisal document.

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 autoantibody-positive systemic lupus erythematosus and the doctor responsible for their care thinks that belimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

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

Anita Sangha
Technical lead

Victoria Kelly and Hannah Nicholas
Technical advisers

Kate Moore
Project manager

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