Final appraisal determination

Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Belimumab is not recommended, within its licensed indication, as add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy.

1.2 People currently receiving belimumab that is not recommended according to 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Belimumab (Benlysta, GlaxoSmithKline) is a human monoclonal antibody that inhibits the activity of B-lymphocyte stimulator (BLyS). Belimumab has a marketing authorisation ‘as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy’.
2.2 According to the summary of product characteristics (SPC), adverse reactions with belimumab include bronchitis, viral gastroenteritis, cystitis, pharyngitis, nasopharyngitis, leucopenia, hypersensitivity reactions, depression, insomnia, migraine, diarrhoea, nausea, pain in extremity, infusion-related reactions and pyrexia. For full details of adverse reactions and contraindications, see the SPC.

2.3 Belimumab is available as a 120 mg or 400 mg powder for intravenous infusion in solution. The recommended dose regimen is 10 mg/kg belimumab on days 0, 14 and 28, and at 4 week intervals thereafter. The SPC states that discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. The list price of belimumab is £121.50 for a 120 mg vial and £405 for a 400 mg vial (excluding VAT; British National Formulary edition 63). Assuming vial wastage, the drug cost per administration for a patient weighing 65–76 kg is £769.50. Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of belimumab has agreed a patient access scheme with the Department of Health, in which a discount on the list price of belimumab is offered. The size of the discount is commercial-in-confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of belimumab and a review of this submission by the Evidence Review Group (ERG; appendix B).
3.1 The manufacturer’s submission focused on a subgroup of the patients whose disease met the criteria specified in the marketing authorisation. The manufacturer explained that, being aware of NHS resources and to identify patients who are most likely to benefit from belimumab, the submission focused on a high disease activity subgroup (hereafter referred to as the target population). The target population is adults with active autoantibody-positive systemic lupus erythematosus with evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10.

3.2 The manufacturer submitted clinical data for all of the patients enrolled in the clinical trials and for the target populations in the trials. Data were presented for both populations individually for each trial and combined across trials. The patient characteristics and results described in the clinical effectiveness section of this document focus on the manufacturer’s target population.

Clinical effectiveness

3.3 The main evidence for the clinical effectiveness of belimumab was from two phase III clinical trials. The BLISS-52 (n = 865) and BLISS-76 (n = 819) trials were randomised, double-blind, placebo-controlled, parallel-group studies with follow-up at 52 weeks and 76 weeks respectively. In these trials, belimumab plus standard care (hereafter referred to as belimumab) was compared with placebo plus standard care (hereafter referred to as standard care). Standard care included: non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, corticosteroids or other immunosuppressants (azathioprine, methotrexate, and mycophenolate mofetil) either alone or in combination. Although
each of the BLISS trials were three-arm trials (belimumab 10 mg/kg, belimumab 1 mg/kg and placebo), only results for the 10 mg/kg belimumab dose were presented in the manufacturer’s submission because this is the dose covered by the marketing authorisation.

3.4 Adult patients (aged 18 years or older) who met the American College of Rheumatology criteria for systemic lupus erythematosus and had active autoantibody positive disease and a SELENA-SLEDAI score of 6 or more at screening were eligible for enrolment in the BLISS trials. Patients with severe active lupus nephritis or central nervous system lupus were excluded from the trials. Of the patients in the standard care and belimumab 10 mg/kg arms (n = 1125), 52% (n = 585) had disease that met the criteria for the marketing authorisation and 35% (n = 396) had disease that met the criteria for the target population.

3.5 The BLISS-52 trial recruited patients from South America, Asia and eastern Europe, whereas the BLISS-76 trial recruited patients from the USA, Canada, Europe (western and eastern) and Israel. In the BLISS-52 trial, approximately 42% of the target population were Asian. In the BLISS-76 trial most of the target population were white (around 65%). Over 90% of the target population included in the trials were women and most (approximately 85%) were aged 45 years or younger. In the target population over 90% of the patients had at least 1A or 1B British Isles Lupus Assessment Group (BILAG) organ involvement and approximately 70% had at least 1A or 2B organ involvement. For the target population mean SELENA-SLEDAI score was approximately 13 in both trials. About 85% of patients in the target population had a physician’s global assessment score of between 1 and 2.5. Most of the patients had a range of manifestations of systemic lupus erythematosus, mainly
involving mucocutaneous, immunological and/or musculoskeletal damage.

3.6 The manufacturer presented results from the BLISS-52 and BLISS-76 trials separately and pooled. The primary outcome of both studies was the response rate at week 52 compared with baseline, assessed with the Systemic Lupus Erythematosus Responder Index (SRI). With the SRI criteria, a response was defined as: a reduction of at least 4 points in SELENA-SLEDAI score (regarded as clinically meaningful); no new BILAG A organ domain score; no more than 1 new BILAG B organ domain score; and no worsening in physician’s global assessment score (increase of less than 0.3).

3.7 For the primary outcome of SRI response at 52 weeks, statistically significant differences were observed between belimumab and standard care in both trials. In the BLISS-52 trial, for the target population, 67% of patients on belimumab had disease that responded compared with 41% of patients on standard care (odds ratio [OR] = 3.0, 95% confidence interval [CI] 1.7 to 5.2). In the BLISS-76 study, for the target population the response was 57% for belimumab compared with 34% for standard care (OR = 2.5, 95% CI 1.3 to 4.6). In the pooled analysis for the target population, 63% of the patients on belimumab had disease that responded, compared with 38% of those on standard care (OR = 2.7, 95% CI 1.8 to 4.1). In the BLISS-76 trial, the target population showed a statistically significant difference in response rate between belimumab and standard care at 76 weeks (p = 0.02).

3.8 For the individual components of the SRI, which were secondary outcomes in the trials, a greater proportion of patients on belimumab in both BLISS trials had a reduction of at least 4 points in SELENA-SLEDAI score compared with standard care. In the
pooled analysis for the target population, 65% of patients on belimumab had a reduction of at least 4 points in SELENA-SLEDAI score compared with 41% on standard care (OR = 2.6, 95% CI 1.7 to 3.9), which was statistically significant. For the outcomes of no new BILAG 1A or 2B organ domain involvement and no worsening in physician’s global assessment, results from BLISS-52 for the target population showed a statistically significant improvement with belimumab compared with standard care, whereas results from BLISS-76 did not. However, there was a statistically significant improvement for both these outcomes in the pooled analysis for the target population.

3.9 For other secondary outcomes, in the pooled analysis of the target population 16% of patients on belimumab compared with 7% of patients on placebo (OR = 2.43, 95% CI 1.05 to 5.65) had an average prednisone dose reduction of greater than or equal to 25% from baseline, to less than or equal to 7.5 mg per day, during weeks 40 to 52. There were no differences in the Systemic Lupus International Collaborating Clinics (SLICC) index of organ damage in the BLISS-52, BLISS-76 or pooled analyses.

3.10 Quality-of-life measures, the SF-36 and EQ-5D, were also collected as secondary outcomes. At week 24 in the pooled analysis of the target population, there was a statistically significant mean change from baseline EQ-5D index for belimumab compared with standard care, but this was not maintained at week 52. The pooled analysis of the target population showed no statistically significant difference in mean SF-36 physical component summary scores between belimumab and standard care at weeks 24 or 52. In the pooled analysis of the target population for functional assessment of chronic illness therapy (FACIT)-fatigue scores, the difference in FACIT-fatigue scores was statistically significant at weeks 8 and 12.
but not thereafter. In the individual trials for the total population, there was a statistically significant difference in FACIT-fatigue scores in favour of belimumab in the BLISS-52 trial at week 52 but not in the BLISS-76 trial.

3.11 In the pooled total trial population, the percentage of people defined as being of African American or African family origin \((n = 100)\) meeting the primary end point was higher in the standard care group (44%) than in the belimumab group (36%). This compared with an overall response rate of 39% in the standard care group and 51% in the belimumab group in the pooled total trial population. For patients of all other family origins, the belimumab group had higher response rates than the standard care group.

3.12 Adverse event data were taken from the total population included in the BLISS trials (that is, not just the target population) and from a phase II extension study (LBSL99). Over 90% of patients in each arm experienced one or more adverse events. The most frequent (occurring in more than 10% of patients) events were headache, upper respiratory tract infection, arthralgia, nausea, urinary tract infection, diarrhoea, and fatigue. Of these events, only diarrhoea and nausea occurred slightly more frequently in the belimumab groups than in the standard care groups. Serious adverse events were experienced by 17% in the 10 mg/kg belimumab group, compared with 16% in the standard care group. Across the double-blind treatment periods, 14 people died, including three (0.4%) in the standard care group, five (0.7%) in the 1 mg/kg group and six (0.9%) in the 10 mg/kg belimumab group. Four deaths were infection-related; one in the standard care group, one in the 1 mg/kg belimumab group and two in the 10 mg/kg belimumab group. Infection may have contributed to the deaths of two further patients (one in the 1 mg/kg belimumab group and one in the
10 mg/kg belimumab group). There were two suicides, both in patients receiving belimumab (one in the 1 mg/kg group and one in the 10 mg/kg group), and one cancer-related death in a patient receiving 1 mg/kg belimumab. In the long-term open-label extension phase of the phase II study, the incidence of adverse events and severe adverse events remained stable or declined over time through 5 years of exposure.

3.13 The manufacturer explained that many patients with severe, highly active systemic lupus erythematosus routinely receive rituximab. No studies were identified that directly compared belimumab with rituximab. However in a study that compared rituximab with placebo (the EXPLORER trial) in patients with moderate-to-severe systemic lupus erythematosus disease activity, no statistically significant differences were reported in major or partial clinical responses between the rituximab group and the placebo group. In addition, the rituximab trial demonstrated no difference in secondary end points between the rituximab group and the placebo group over 52 weeks. The manufacturer stated that differences in the end points considered and the patient populations precluded any meaningful indirect comparison between the belimumab and rituximab studies.

**Cost effectiveness**

3.14 A de novo decision-analytic model was developed by the manufacturer. The model is a micro-simulation that incorporates the interaction between patient characteristics, disease activity, medication (corticosteroid use), risk of organ damage development (a patient with systemic lupus erythematosus could potentially develop damage in 12 different organ systems) and mortality. The manufacturer presented results on the target population as well as the proportion of patients in the trial whose disease met the criteria...
in the marketing authorisation (hereafter referred to as the marketing authorisation population) and total trial populations. The model results presented here focus on the target population.

3.15 The health states in the model were informed by data from the BLISS trials, observational cohort data (the Johns Hopkins cohort, see 3.17), and other data from the literature. A patient’s baseline characteristics were simulated based on the pooled target population characteristics in the BLISS trials. The BLISS clinical trials were used to inform the likelihood of response at week 24 (based on a patient demonstrating a SELENA-SLEDAI score decrease of 4), the change in SELENA-SLEDAI score up to week 52, the likelihood of discontinuation, and the effect of SELENA-SLEDAI score on utility and treatment costs. Data from the literature were used to inform the standardised mortality rate for a given SELENA-SLEDAI score, and quality of life and cost impacts of long-term damage to each organ system.

3.16 The patient entered the model in which their lifetime history of systemic lupus erythematosus was simulated, based on the BLISS trial data. A patient's characteristics were ‘cloned’ so that the same modelled ‘patient’ entered both standard care plus belimumab 10 mg/kg (hereafter referred to as belimumab) and standard care only (hereafter referred to as standard care) treatment paths and then worked through the model. For a patient entering the model assigned to either belimumab or standard care, it was first determined whether the patient survived for that year. A surviving patient on belimumab could then either continue with belimumab treatment or discontinue treatment. The treatment discontinuation rate was calculated from the BLISS trial data. Patients discontinued treatment after week 24 if they did not have an improvement in SELENA-SLEDAI score of 4 points or more. An annual
discontinuation rate in patients whose disease responded to
treatment was estimated to be 8% per year.

3.17 Prediction models based on data from the Johns Hopkins cohort
were used to predict change in adjusted mean SLEDAI (AMS)
score (which is used as a proxy for SELENA-SLEDAI score),
average steroid dose per year, risk of organ damage and risk of
death. The Johns Hopkins cohort reported data on a large
population of patients with systemic lupus erythematosus from
Baltimore, Maryland, USA of whom 93% were women, 52% were
white and 38% were black. Analyses were conducted on a dataset
of 1282 people, with follow-up of greater than 2 years and data
after 1992. Mean age at diagnosis was 33 years and mean SLEDAI
score at first visit was 3.32.

3.18 In the first year of the simulation, the effects on disease activity as
observed in the BLISS trials were applied, measured by SELENA-
SLEDAI score. A linear regression model based on data from the
BLISS trials was used to predict the change in SELENA-SLEDAI
score at 52 weeks. For subsequent cycles, disease activity was
predicted using regression equations based on the natural history
data from the Johns Hopkins cohort. Because the baseline
characteristics from the Johns Hopkins cohort were different from
the patient characteristics in the pooled BLISS trials (patients in the
Johns Hopkins cohort had lower disease activity than those in the
BLISS trials), the manufacturer adjusted the constant in the
regression to obtain a better fit to the data.

3.19 Steroid use was calculated based on a regression equation from
the Johns Hopkins cohort, with disease activity as measured by
mean SLEDAI score as the sole independent variable. For each
organ system contained within the SLICC Damage Index, the
probability of damage during that year was calculated based on the
patient’s characteristics and disease activity at that time. The manufacturer also developed a survival model using the Johns Hopkins cohort, adjusting it by standardised mortality ratios from the literature. Average costs and utilities calculated from regression analyses were assigned to a patient’s health state for that particular year. Costs and utilities were recorded together with clinical outcomes for that patient. Time was then increased by 1 year and the process was repeated for the lifetime of the patient. These yearly cycles continued until a patient died. Utilities and costs were discounted at 3.5%. An NHS and personal social services perspective was adopted. Adverse events were not included in the model.

3.20 The baseline quality of life assumed in the cost-effectiveness analysis was determined by a regression equation (which accounted for age, family origin and SELENA-SLEDAI score), which was derived from the BLISS trials. Disutility multiplier values for each type of organ damage were identified from a search of the literature. These disutility multipliers were applied to the utility score if a patient developed organ damage in the model cycle. Costs in the analysis were limited to direct medical costs and costs associated with disease activity and long-term organ damage. Total resource use varied according to disease severity and was determined using a linear regression analysis. A literature search was conducted to identify the cost of organ damage. All costs were inflated to 2010 values. The base case considered only the additional acquisition costs for belimumab. Because belimumab is given in addition to standard care, it was assumed that the costs for standard care treatments would be the same for people on belimumab as for those not on belimumab and so were not included. The administration cost of £126 for belimumab was calculated based on 2 hours of senior hospital staff nurse time.
(£63 per hour): 1 hour for the infusion and another 1 hour for patient preparation and monitoring post-infusion. It was assumed that the first year annual cost of treatment and administration of belimumab was £10,918 and in subsequent years £10,138, based on a cost of belimumab of £114.30 for a 120 mg vial and £381 for a 400 mg vial. At the time of submission, the vial price for belimumab had not been finalised, so the expected vial list price was used in the base-case analyses. The effect on cost effectiveness of a maximum expected vial price for both the 120 mg and 400 mg vials was investigated in a scenario analysis. The inclusion of a cost for standard care and different costs of administration were also explored in scenario analyses.

3.21 The model showed lower disease activity for patients on belimumab than in patients on standard care only, which led to decreased steroid dose and decreased risk of organ damage and contributed to a difference in mortality risk. The model predicted that patients on belimumab live longer than those on standard care. Although a decreased duration of damage was shown for organs on which belimumab has a large effect (cardiovascular, pulmonary and renal), the duration of damage for other organ systems is increased because of the prolonged life expectancy.

3.22 The model predicted that patients treated with belimumab, in the target population, live on average 2.9 years longer (34.9 compared with 31.9 years), have a reduction in average adjusted mean SLEDAI score, reduced cumulative monthly steroid dose and similar total SLICC organ damage score compared with those on standard care only. Treatment with belimumab provided an estimated additional 1.1 life years and 0.8 quality-adjusted life years (QALYs) (both discounted values). For both treatment groups, the organ damage costs were the highest expense. In total,
the organ damage costs were lower for patients treated with belimumab. The costs related to disease activity were similar in the two treatment arms. Because of their increased life expectancy and the cost of belimumab treatment, costs were higher for patients receiving belimumab than for those on standard care.

3.23 For the target population, not including the patient access scheme, total costs were £157,291 for belimumab and £105,366 for standard care. Total QALYs were 10.61 for belimumab compared with 9.81 for standard care. The incremental costs were therefore £51,925, and the incremental QALYs 0.806. This resulted in an incremental cost-effectiveness ratio (ICER) of £64,410 per QALY gained. The probabilistic sensitivity analysis results showed that at a threshold of £30,000 per QALY gained, there is a 0% probability that belimumab is cost effective compared with standard care.

3.24 In comparison, the ICER for the marketing authorisation population was £66,170 per QALY gained (undiscounted life years gained of 2.1 years, reflecting a difference in estimated survival of 35.0 compared with 32.8 years). The ICER for the total trial population (which included a wider population than that specified in the marketing authorisation) was £82,909 per QALY gained.

3.25 In sensitivity analyses conducted in the target population analysis, factors affecting cost effectiveness were: the treatment effect regression to estimate the effect of belimumab after 52 weeks, the size of the manufacturer’s adjustment to the constant of the disease activity prediction equation, the probability of discontinuation, the effect of the adjusted mean SLEDAI score on mortality, and the natural history models for pulmonary and renal involvement. Scenario analyses were conducted, with resulting ICERs ranging from £50,114 to £77,707 per QALY gained. Removing the continuation rule increased the ICER to £72,207 per
QALY gained, and increased vial prices of £127.80 for the 120 mg vial and £426 for the 400 mg vial (the maximum expected vial price) resulted in an ICER of £71,297 per QALY gained.

3.26 The patient access scheme comprises a simple discount, which was accepted by the Department of Health and incorporated into the analysis of belimumab compared with standard care. An ICER with the patient access scheme was provided. However, the level of the discount and the results from the economic analysis incorporating the patient access scheme are commercial-in-confidence.

3.27 A comparison of the costs of belimumab and rituximab, taking into account the patient access scheme, was also provided by the manufacturer. The manufacturer calculated the cost of rituximab from the administration schedule used in the EXPLORER trial. A course of rituximab was 1000 mg, provided on days 1, 15, 168 and 182. The total drug cost of rituximab was £6985 per year.

**Further evidence submitted by the manufacturer after the first Appraisal Committee meeting**

3.28 In response to consultation, the manufacturer presented long-term efficacy and safety trial data from the open label, phase II extension study (LBSL99; Petri et al. 2011) for belimumab, which suggested continued efficacy with belimumab and safety over a 6-year follow-up period. Patients with seropositive disease treated with belimumab showed sustained improvement in disease activity and a decline in BILAG scores and flares over 6 years, accompanied by reductions in corticosteroid use and autoantibody levels. The abstract provided by the manufacturer showed a mean reduction in steroid use of 4.7 mg per day, an average reduction of 34.4% from the baseline dose, by the end of 6 years of follow-up. An annual
discontinuation rate of approximately 13% was also observed in this trial.

3.29 As well as further clinical evidence, in response to consultation the manufacturer submitted additional cost-effectiveness evidence using the same assumptions as in the original base-case model, but incorporating a maximum treatment duration of 6 years and using the confirmed list price for belimumab. The manufacturer’s revised base case resulted in an ICER of £47,342 per QALY gained, with an incremental cost of £28,705 and incremental QALY of 0.61. In a scenario analysis conducted by the manufacturer on the revised base-case analysis, the continuation rule for belimumab was changed from a SELENA-SLEDAI score of greater than or equal to 4 to greater than or equal to 6 and the health effects discount rate lowered from 3.5% to 1.5%. These scenarios had the effect of lowering the ICER to £40,863 and £31,988 per QALY gained respectively. When both scenarios were applied together, they lowered the ICER to £27,807 per QALY gained, with an incremental cost of £20,766 and incremental QALY gained of 0.747.

3.30 The manufacturer stated that the change from an unlimited treatment duration to a maximum of 6 years was made in response to comments in the appraisal consultation document about the need to align the use of belimumab more closely with how clinicians would consider using belimumab in clinical practice. While recognising the lack of any direct evidence about optimal treatment duration, the manufacturer supported the use of belimumab up to a duration of 6 years with the newly available long-term data for belimumab from the phase II extension study (see section 3.28). The manufacturer also explained that other treatments for systemic lupus erythematosus, such as
immunosuppressants, are prescribed for 2–5 years to maintain suppression of disease activity. The manufacturer stated that it believed that 6 years of treatment with belimumab was long enough for the benefits of belimumab on controlling high disease activity to have an important impact on reducing long-term morbidity.

3.31 According to the manufacturer it was appropriate to use NICE's clarification to section 5.6 of the Guide to methods of technology appraisals on the discounting of health benefits in special circumstances for a number of reasons. These were because of the nature of systemic lupus erythematosus and the fact that belimumab has been shown to result in clinically important reductions in disease activity, and has the potential to provide important long-term benefits including reduced organ damage, reduced use of high-dose steroids, along with their associated risks, and consequently improved survival. Therefore, the manufacturer considered that the discount rate of 1.5% for health effects rather than the 3.5% normally applied in technology appraisals was appropriate. Further, the manufacturer stated that by applying a continuation rule at 24 weeks of a SELENA-SLEDAI score greater than or equal to 6 rather than 4, a more efficient use of NHS resources could be made.

Evidence Review Group comments on the original submission

3.32 The ERG stated that the marketing authorisation population and the target population that formed the focus of the submission were subgroups identified from post-hoc analyses aimed at identifying patients with the greatest response to belimumab. The ERG noted that according to clinical opinion the SELENA-SLEDAI (a component of the SRI and one of the measures used to identify people in the target population) is not commonly used to define high disease activity in clinical practice.
3.33 The ERG commented that although both trials included adults with active autoantibody-positive systemic lupus erythematosus, the population in BLISS-76 is more likely to be similar to that of England and Wales than that of BLISS-52, so the results from BLISS-76 are more likely to be generalisable to the UK. This was because the differences in geography and family origin between the patients in the trials were considered to potentially affect the results of the trials as well as reflecting differences in clinical practice. The ERG stated that, for the target population, the results from the BLISS-52 trial were more favourable for belimumab than those from BLISS-76, and BLISS-52 provided more patients to the pooled target population than BLISS-76 (55% compared with 45%). Therefore, results favourable to belimumab for the pooled target population were more strongly driven by the contribution from the BLISS-52 target population. The ERG, therefore, had concerns about the relevance of the pooled results for patients in England and Wales.

3.34 The ERG highlighted that information on SLEDAI and SF-36 changes in the rituximab EXPLORER trial were available, and that randomised controlled trials for both rituximab and belimumab recorded BILAG scores changes.

3.35 The ERG considered that the manufacturer’s model was complex, though generally well constructed. It noted that the model conformed to the NICE reference case and that the longer-term effects of systemic lupus erythematosus had been modelled well, using the Johns Hopkins cohort. An ERG cross-check of the probabilistic modelling for the target population resulted in a central estimate of £65,530 per QALY gained.

3.36 The ERG commented that there was a lack of clarity around the reasons for patients’ discontinuation of belimumab, the derivation of
the 8% annual discontinuation rate among patients showing a response to belimumab at week 24, and whether extrapolation using this value was reasonable. Sensitivity analyses by the manufacturer showed that a low discontinuation rate, such as 2%, increased the ICER for belimumab to £85,893 per QALY gained, whereas a higher discontinuation rate, such as 14%, reduced the ICER to £54,518 per QALY gained.

3.37 The ERG stated that the model assumed that patients whose disease had not responded to belimumab by week 24 (one third of patients) experienced the average SELENA-SLEDAI score seen with standard care (which includes approximately equal proportions of patients whose disease had responded and patients whose disease had not responded in the pooled target population). The ERG considered that this assumption is likely to overestimate the average impact on SELENA-SLEDAI scores in the belimumab arm, both between week 24 and 52 and beyond week 52, leading to an underestimation of the ICER.

3.38 The ERG noted that the adjusted mean SLEDAI score contributed to the likelihood of a patient dying and of a patient developing particular organ involvement. The economic modelling did not take into account a patient's history before entry into the trial and this may also have exaggerated the impact that changes in SELENA-SLEDAI score had on the adjusted mean SLEDAI score for belimumab compared with standard care, with the likely result that the base-case ICER was an underestimate. This is potentially important when comparing the Johns Hopkins cohort, in which most patients had SELENA-SLEDAI scores of less than ten, with the target population, who all had scores of greater than ten at baseline.
3.39 The ERG stated that the reason for adjusting the Johns Hopkins cohort survival model by standardised mortality ratios from the literature was unclear and may have tended to exaggerate the impact of the individual covariates within the Johns Hopkins cohort survival model. Unpublished data from a UK study obtained by the ERG also suggested that the standardised mortality ratios used by the manufacturer may not accurately represent a UK cohort. An exploratory analysis using the lower standardised mortality ratios derived from the UK study increased the ICER by approximately £6000 to £70,860 per QALY gained.

3.40 The ERG highlighted that the constant in the SELENA-SLEDAI change regression equation from the Johns Hopkins data was originally 2.0577 but was adjusted by the manufacturer to 3.0 to improve the fit to belimumab trial data after week 52. Sensitivity analyses by the manufacturer showed that using the original value of the constant term increased the ICER by approximately £29,000, to £93,654 per QALY gained.

3.41 The ERG considered the impact of using different administration costs than those used in the model (£126). The ERG’s exploratory analysis found that if costs were in line with those from a previous appraisal of another intravenous monoclonal antibody drug (‘Tocilizumab for the treatment of rheumatoid arthritis’ [NICE technology appraisal guidance 247; rapid review of technology appraisal guidance 198]), which had a similar duration of administration and an administration cost of £154, then the ICER would increase by approximately £2500 to £66,907 per QALY gained. If the full day-case cost was used (£432) then the ICER would be higher by approximately £27,000, at £91,699 per QALY gained.
3.42 The ERG completed an exploratory analysis that used the estimates from the single trials in the disease activity regression equation rather than the pooled estimate. This analysis demonstrated that the economic model was not particularly sensitive to the use of single estimates. Using BLISS-76 as the source of the regression increased the ICER by approximately £2000 to £66,318 per QALY gained.

Critique by the ERG of the manufacturer’s new evidence provided after the first Appraisal Committee meeting

3.43 The ERG commented on the new evidence provided by the manufacturer about the long-term steroid sparing effect of belimumab. The ERG noted that the basis of the calculations was not clear and the ERG questioned whether the average baseline steroid use was calculated for the same patients in whom steroid use was estimated at 6 years. The ERG stated that the manufacturer proposed that the steroid sparing effect, together with other belimumab benefits such as reduced flare frequency, would reduce the development of organ damage and would therefore translate into long-term benefit. However, the ERG stated that data are only available for 6 years, which indicates that there is a substantial degree of uncertainty over whether the effects observed in the data would translate into longer term effects.

3.44 The ERG reviewed and critiqued the manufacturer’s additional economic analysis submitted after consultation. The ERG noted that the manufacturer’s revised base-case model was based on 6 years maximum treatment duration, while the original model had some patients receiving treatment for 40 years. The ERG considered that the maximum duration of belimumab treatment was uncertain because clinical opinion is likely to vary. The ERG stated that the manufacturer’s revised base-case model also assumed
that while the SELENA-SLEDAI scores for the patients at the end of year six revert to scores expected for patients receiving standard care, the AMS score continues to show benefit, which could indicate a sustained reduction in organ damage in the treatment arm. The ERG also noted that given an annual discontinuation rate of 8% (as in the original submission) or the rate observed in the phase II extension study (13% annual discontinuation rate), if a maximum treatment duration of 6 years was imposed, a considerable number of patients receiving benefit from belimumab would have treatment withdrawn. The ERG calculated that of 339 patients receiving belimumab at the end of the second year of treatment in the phase II extension study, 167 were still receiving treatment at the end of the sixth year. The ERG commented that the manufacturer did not address tapering off rules, the issue of potential rebound phenomena, the ethical considerations of withdrawing treatment or the possibility of reintroducing treatment and the effect of this on cost effectiveness.

3.45 The ERG evaluated the continuation rule used in the analyses. The ERG observed that changing the continuation rule so that a minimum SELENA-SLEDAI improvement of 6 is needed to continue treatment reduces the benefits the patients receive from belimumab, but it accordingly reduces costs and the ICER by a greater proportion than when a continuation rule of a minimum SELENA-SLEDAI improvement of 4 is applied.

3.46 The ERG noted that the manufacturer suggested that belimumab treatment for systemic lupus erythematosus should be appraised using a 1.5% discount rate for health benefits. The ERG noted that the evidence presented showed a beneficial response to belimumab lasting at least 6 years in an appreciable population of patients. The ERG noted that the manufacturer considered that this
early effect of belimumab, together with the observed 34% reduction in steroid usage, would translate into long-term benefit by reducing the development of organ damage. The ERG commented that the extent to which short-term benefits translated into longer-term benefits was uncertain and presented data showing that in the economic modelling 63% of the incremental QALY gain (undiscounted) was accrued within 30 years.

3.47 The ERG completed additional analyses, applying a lifetime treatment duration and a maximum 6 year treatment duration. For both of these, separate scenarios were modelled that assumed no continuation rule at 24 weeks, a continuation rule at 24 weeks of SELENA-SLEDAI score greater than or equal to 4 and a continuation rule at 24 weeks of SELENA-SLEDAI score greater than or equal to 6. These analyses also assumed an annual discontinuation rate of 13% after 24 weeks and an administration cost of £154 as had been used in previous appraisals of intravenous monoclonal antibody treatments for rheumatoid arthritis. Benefits and costs were discounted at 3.5%. Analyses were presented both with and without the patient access scheme.

3.48 Assuming a lifetime treatment duration for belimumab, the ICERs without the patient access scheme were £90,002, £61,193 and £53,744 per QALY gained for the scenarios assuming no continuation rule at 24 weeks, a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater than or equal to 4 and a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater than or equal to 6, respectively. The incremental costs in these scenarios were £57,526, £40,499 and £31,878 respectively and incremental QALYs 0.639, 0.662 and 0.593 respectively. ICERs with the patient access scheme were provided. These were
marked commercial-in-confidence because of the confidential nature of the patient access scheme.

3.49 Assuming a maximum 6 year treatment duration for belimumab, the ICERs without the patient access scheme were £70,942, £47,382 and £42,108 per QALY gained for the scenarios assuming no continuation rule at 24 weeks, a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater or equal to 4 and a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater or equal to 6, respectively. The incremental costs in these scenarios were £37,888, £26,300 and £21,104 respectively and incremental QALYs 0.534, 0.555 and 0.501 respectively. ICERs with the patient access scheme were provided. These were marked commercial-in-confidence because of the confidential nature of the patient access scheme.

3.50 Full details of all the evidence are in the manufacturer’s submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of belimumab, having considered evidence on the nature of active autoantibody-positive systemic lupus erythematosus and the value placed on the benefits of belimumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the nature of the condition, and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical signs and symptoms associated
with systemic lupus erythematosus. The Committee heard from clinical specialists and patient experts how this disease is a debilitating condition, primarily affecting younger women. It affects daily life, including the ability to work and to have children. The clinical specialists explained that people with systemic lupus erythematosus tend to die younger than the average population. The Committee heard that there are very few licensed treatments for the disease and that patients would welcome an additional treatment option specifically for this disease. Further, it was highlighted that many patients have to take several different drugs daily and that any treatment that might reduce this number would be welcomed. Reduced side effects of other drugs, especially corticosteroids, would also be welcome. The Committee recognised the importance of the availability of treatment options for people with systemic lupus erythematosus and the need to reduce the side effects of immunosuppressants in current use.

4.3 The Committee discussed the likely position of belimumab in clinical practice. The Committee noted that standard care is likely to consist of non-steroidal anti-inflammatory drugs, corticosteroids, antimalarials or immunosuppressants. It also noted that the marketing authorisation for belimumab states that it should be used for patients with high disease activity ‘despite standard therapy’. The Committee heard from clinical specialists that 10–15% of patients continue to have high disease activity despite standard therapy, and that a proportion of these are currently treated with rituximab, frequently through individual funding requests. The Committee understood that rituximab is used in people with severe disease to reduce the levels of disease activity (that is, to induce remission) and to reduce the amount of steroids and other immunosuppressants prescribed. The Committee also heard from the clinical specialists that rituximab treatment is repeated in such
patients when the disease shows signs of a significant increase in activity and that the re-treatment interval with rituximab varies from patient to patient. The clinical specialists explained that they considered that rituximab would be a relevant comparator for the group of people for whom belimumab was indicated. The Committee therefore concluded that both rituximab and standard care were relevant comparators, as specified in the final scope and in the manufacturer’s decision problem. The Committee was also aware that cyclophosphamide was also included as a comparator in the scope, but noted the manufacturer’s justification that it was largely used for lupus nephritis, which was a different population to the one included in the trials of belimumab and covered by the marketing authorisation for belimumab. Further, it heard from clinical specialists that cyclophosphamide is used infrequently because of side effects.

4.4 The Committee discussed how belimumab would be used in clinical practice and heard from the clinical specialists that continuous use of belimumab for a long time would be very unlikely. The clinical specialists explained that one of the aims of treatment with belimumab would be to work towards coming off the treatment. Once a patient was in remission, belimumab treatment would be gradually stopped by reducing its frequency or dose. Serological activity would be monitored and belimumab treatment restarted if a patient became symptomatic or if the serological tests signalled that this was likely. The manufacturer explained that there were no data available that reflected the scenarios described by the clinical specialists, such as treatment holidays or tapering of treatment. However, the Committee noted that the European Medicines Agency has requested that the manufacturer address uncertainties about the effect of stopping treatment with belimumab (treatment holidays) as well as the risk of rebound phenomena, as part of the
routine pharmacovigilance programme. The Committee was aware that in the SPC belimumab is indicated as an add-on treatment in patients with a high degree of disease activity despite standard therapies and it also observed that the European Medicines Agency’s European public assessment report for belimumab acknowledged that the BLISS studies were not designed for inducing remission, but rather for maintenance therapy. In addition the Committee noted that the data supporting longer term use of belimumab used a continuous schedule of administration over 6 years in patients whose disease responded to treatment. Although the manufacturer had presented data supporting the continuous use of belimumab in patients whose disease responded, the Committee concluded that in clinical practice belimumab might be used in the same intermittent way as rituximab although no efficacy data that reflects this use of belimumab is available.

4.5 The Committee discussed the population in the manufacturer’s decision problem. It noted that the manufacturer focused on a target population who were a subgroup of the population covered by the marketing authorisation and the BLISS clinical trials. The target population was identified by a SELENA-SLEDAI score of greater than or equal to 10 and evidence of serological disease activity. The Committee noted that although a SELENA-SLEDAI score of greater than or equal to 10 had been a pre-specified stratification factor in the BLISS clinical trials, when combined with the marketing authorisation criterion of a high degree of serological disease activity, this was not a group that had been pre-specified in the BLISS clinical trials. However, the Committee heard from the clinical specialists that although the SELENA-SLEDAI score was not currently used in clinical practice to measure disease activity, people with a SELENA-SLEDAI score of greater than or equal to 10
would be those with clinically significant disease likely to be considered for treatment with belimumab. The Committee also noted comments from consultation that a more routine use of the SELENA-SLEDAI score in clinical practice could improve the management of systemic lupus erythematosus. The specialists also explained that the biomarkers mentioned in the marketing authorisation (that is, low complement and positive anti-double stranded DNA antibody test), would be used for demonstrating evidence of serological disease activity and would detect changes in disease activity. The Committee concluded that though specifying a SELENA-SLEDAI score of greater than or equal to 10 may be considered arbitrary, the specified target population is clinically relevant.

**Clinical effectiveness**

4.6 The Committee discussed the manufacturer’s submission of clinical evidence, noting that most of the evidence in the manufacturer’s submission was from the two BLISS trials (BLISS-52 and BLISS-76) that compared belimumab against standard care. The Committee considered the composite end point of the SRI used in the BLISS trials. It noted that this end point was developed in conjunction with the Food and Drug Administration in the USA. The Committee heard from the clinical specialists that the SELENA-SLEDAI score, a component of the SRI, is a relatively crude tool and that the specialists considered the use of the composite tool, which also includes the BILAG tool (as well as the physician’s global assessment), was reasonable. The Committee accepted the evidence from the clinical specialists that the SRI was an appropriate outcome in the trials.

4.7 The Committee discussed whether the individual BLISS trials were representative of the UK population, in particular, whether data
from the BLISS-52 trial were as relevant to UK practice as data from the BLISS-76 trial. The Committee noted that the BLISS-52 trial recruited people from eastern Europe, South America and Asia, and that the BLISS-76 trial recruited people from Europe (western and eastern), the USA, Canada and Israel. The clinical specialists explained that because the UK is a multi-ethnic country and systemic lupus erythematosus affects many ethnic groups more severely than white populations, data from different populations would still be relevant to the UK. Further, the Committee understood from the clinical specialists that clinical practice varies between countries, for example in the USA higher doses of steroids are used than in the UK. Therefore, there may also be issues about the relevance of the data from BLISS-76. On balance, the Committee concluded that BLISS-76 was more representative of the population of England and Wales than BLISS-52. However, data from BLISS-52, and therefore from the pooled analysis would be relevant.

4.8 The Committee discussed the characteristics of the patients in the BLISS trials. It noted that the patients in the BLISS trials had mainly immunological, mucocutaneous and musculoskeletal manifestations of systemic lupus erythematosus at baseline. The Committee noted comments from consultation that the range of manifestations in the BLISS clinical trials was similar to those in clinical practice in the UK. Further, it noted comments that serological manifestations are indicative of wider systemic disease activity. The Committee discussed whether, on this basis, belimumab may be expected to also show benefits for other manifestations. The Committee heard from clinical specialists that if the experience of belimumab was like rituximab, then benefits for the range of manifestations may be expected. However, there remained uncertainty, and initially belimumab may be more likely to
be used in people with predominantly musculoskeletal and mucocutaneous involvement. The Committee concluded that currently the effect of belimumab on the full range of manifestations of systemic lupus erythematosus was uncertain.

4.9 The Committee discussed baseline standard care in the two BLISS trials. It noted variations in the treatments people were receiving at baseline and that approximately 50% of people were receiving an immunosuppressant. The Committee understood there was variability in clinical practice in the use of such drugs. However, it heard from the clinical specialists that, in the UK, people for whom treatment with belimumab would be considered would have active disease despite standard therapy, and that standard therapy for most people would include an immunosuppressant. The Committee concluded that there was uncertainty about the extent to which standard care in the belimumab trials represented UK clinical practice, for the target population for whom belimumab is intended.

4.10 The Committee discussed the results of the BLISS trials and noted that although in the individual trials the difference between the two arms for the primary outcome (the SRI) was statistically significant, the difference between the two arms for the components of the SRI were not statistically significant in BLISS-76, with the exception of the SELENA-SLEDAI outcome. The Committee also discussed the evidence of steroid sparing, noting that a statistically significant reduction in steroid use was observed in the pooled analysis. The Committee noted the absolute reduction in use was about 1 mg per day in the model. The Committee discussed the health-related quality of life outcomes in the clinical trials (EQ-5D and SF-36) and noted that at week 52, no statistically significant differences between the treatment groups were reported in either trial, for the target population. The Committee also noted that the difference
between the two arms for the FACIT-fatigue scores was not statistically significant at week 52 in the target population. The Committee concluded that compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the evidence of effect was observed with greater consistency across outcomes in the BLISS-52 trial. Further, the relevance of both the pooled and unpooled data to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, nature of standard care and effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus (see sections 4.7, 4.8 and 4.9).

4.11 The Committee discussed the long-term data provided by the manufacturer from the extension of the phase II study. The Committee recognised that this study had been provided by the manufacturer primarily as additional evidence about long-term reduction in steroid dose, but noted that data from the study suggested continued clinical benefit from belimumab treatment over a 6-year period. The Committee first discussed the data for reductions in steroid dose, noting that these showed an absolute reduction in steroid dose at 6 years of 5 mg a day. The Committee then noted the sustained improvement over 6 years in measures of disease activity (such as the SRI response rate, reduced autoantibody and complement levels) and the reduced frequency of disease flares. The Committee considered that in the absence of a control group, the phase II data were unable to definitively demonstrate the clinical benefits of continuous belimumab treatment for patients whose disease responded, but the data were suggestive of continuing benefit. The Committee heard from the ERG that the reduction in steroid use modelled in the economic analyses showed an absolute change in steroid use for belimumab that was similar to the reduction seen in the phase II extension.
study. The Committee concluded that these data suggested, but were not definitive proof of a reduction in steroids associated with belimumab treatment. However, the Committee understood the importance of reductions in steroid dose for patients and recognised the positive indications of these findings.

4.12 The Committee explored the comparison of belimumab with rituximab and the evidence available to support the comparison, noting that head-to-head data comparing belimumab with rituximab were not available. It discussed the available evidence of rituximab compared with placebo from the EXPLORER trial and considered whether any indirect analysis could be conducted. The Committee heard from the clinical specialists that the EXPLORER trial included patients with more severe disease (that is, in terms of steroid use and dose and existing organ damage) than those in the BLISS studies, so the trial populations were different. The Committee heard from the ERG that there were three outcomes for which an indirect comparison could be completed (that is, BILAG, SLEDAI and SF-36 scores), but data were only available in the public domain for the SF-36. The ERG also highlighted the differences in the trial populations, which it considered meant that the results of an indirect comparison were not meaningful. The Committee concluded that there are no reliable data to show the relative efficacy of belimumab compared with rituximab.

Cost effectiveness

4.13 The Committee discussed the economic model submitted by the manufacturer that informed both the original and revised analyses. The Committee noted that short-term outcomes from the BLISS studies were linked to long-term outcomes, using data from the Johns Hopkins cohort. The Committee considered the similarity of people in the Johns Hopkins cohort to those in the BLISS trials and
noted that the people in the BLISS trials had higher SELENA-SLEDAI scores than the average SLEDAI scores in the Johns Hopkins cohort, indicating that the populations in the trials had more active disease than in the Johns Hopkins cohort. The Committee noted that the SLEDAI scores from the Johns Hopkins cohort were used to inform the equation for disease activity, steroid use, mortality and organ involvement, but that only the equation for disease activity was adjusted so that it more closely matched the BLISS trial populations. The Committee heard from the manufacturer how the model was driven by changes in the SELENA-SLEDAI score based on data from the Johns Hopkins cohort and that cost effectiveness was not particularly driven by other factors, such as by steroid use. The Committee accepted that attempting to link short-term outcomes to long-term outcomes was appropriate and recognised that there were limited data sources available with which to do this. However, it concluded that there was uncertainty about whether the equations derived from the Johns Hopkins data could be reliably applied to the target population because of differences in study populations.

4.14 The Committee discussed the effects that the expected annual discontinuation rates for belimumab after the first 24 weeks, assumed in the original and revised models, had on the cost effectiveness of belimumab. The Committee noted that in the original model the manufacturer had assumed an 8% annual discontinuation rate after 24 weeks, based on data from the BLISS trials. In the manufacturer’s additional evidence provided after consultation, longer term data were provided from the phase II extension study, which showed an annual discontinuation rate of 13%. The Committee noted the manufacturer’s analysis in their original submission, which showed that a low discontinuation rate, such as 2%, increases the ICER to £85,900 per QALY gained, and
a higher discontinuation rate of 14% improves it to £54,500 per QALY gained. The Committee questioned whether the discontinuation rate in the phase II extension study may have been higher because of the lower baseline disease activity observed in the patients in the study compared with the target population from the BLISS trials. It also noted that the reasons for discontinuation in the phase II extension study were not described. However, the Committee concluded that the manufacturer may have underestimated the annual discontinuation rate in the original economic model, and therefore overestimated the ICER, and that a higher rate of annual discontinuation as observed in the phase II extension study may be more appropriate.

4.15 The Committee again discussed the expected duration of use of belimumab in clinical practice, noting that that the original model predicted continuous treatment with belimumab for some people over the course of 40 years. The Committee had concluded that continuous treatment over many years was unlikely to reflect how belimumab would be used in clinical practice (see section 4.4). However, it was aware that the SPC for belimumab describes continuous use and noted the manufacturer’s statements that there were no data available to model treatment holidays or tapering of treatment. In addition, the Committee noted that the data for longer term use of belimumab were for a continuous schedule of administration in patients whose disease responded to treatment and the manufacturer’s original and revised economic models used continuous treatment for potentially lifelong and 6 year durations of treatment, respectively. The Committee was therefore unable to make recommendations taking into account intermittent treatment or alternative administration schedules because there was neither efficacy data that reflected this use of belimumab nor any evidence of the cost effectiveness of such an approach.
4.16 The Committee discussed the revised analyses presented by the manufacturer, which assumed continuous treatment, but limited to the maximum treatment duration of 6 years. The Committee heard from the manufacturer that taking into consideration the evidence from clinical specialists at the first Committee meeting and from other consultation with clinicians, it was clear that it was likely that in clinical practice belimumab would not be used continuously over a lifetime. The manufacturer explained that the only long-term data available on which to base treatment duration were the 6-year data from the phase II extension study, hence the choice of 6 years. The Committee heard from the clinical specialists that because of the heterogeneity of systemic lupus erythematosus, some patients may require treatment continuously for longer than 6 years. But for most, it was more probable that belimumab would be used for less than 6 years until a patient’s disease was in remission. The Committee considered the implications of stopping belimumab treatment at 6 years. The Committee noted that the data from the phase II extension study suggested there could be a possibility of continued benefit with continued treatment at 6 years, because approximately 50% of patients on treatment with belimumab at the end of the second year were still on it at the end of the sixth year. The results of this study therefore suggested a rationale for continued use of belimumab in a significant proportion of patients beyond 6 years. The Committee concluded that although the 6 year maximum treatment duration modelled in the manufacturer’s revised analyses improved the cost effectiveness of belimumab, the rationale for the choice of a maximum treatment duration of 6 years could not be considered sufficiently robust for use as the basis of decision making.

4.17 The Committee considered the continuation rules applied in the economic model, noting that the SPC states that discontinuation of
treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. The Committee noted that the original economic model applied a rule that patients would continue treatment after week 24 if there was an improvement in their SELENA-SLEDAI score of 4 points or more, and that after consultation an additional analysis using a more stringent rule requiring an improvement of 6 points or more on the SELENA-SLEDAI scale had been proposed by the manufacturer. The Committee heard from the clinical specialists that if the patient had not shown any benefit from treatment with belimumab after 6 months of treatment, then they would be likely to discontinue treatment as per the SPC. The Committee heard that the clinical specialists indicated that a gain of 4 points on the SELENA-SLEDAI score was generally considered to be a reasonable improvement and that if there was some benefit of treatment at 24 weeks, but less than 4 SELENA-SLEDAI points, the patient may continue treatment with belimumab. The Committee then discussed the difference between the 4 and 6 point continuation rules and heard from the clinical specialists that they would prefer the lower continuation rule of an improvement of 4 points in the SELENA-SLEDAI score, and would be uneasy using the higher continuation rule of 6 points unless it reduced the base-case ICER to an acceptable level. The Committee discussed the additional analyses provided by the ERG, noting that the ICERs were only modestly sensitive to the application of different continuation rules, but on their own did not reduce the ICERs in the Committee’s preferred base-case analyses to a level considered to be cost effective. The Committee noted that the ICERs provided by the ERG without the patient access scheme for belimumab assuming lifetime treatment were £61,200 and £53,700 per QALY gained for the scenarios with a continuation rule at 24 weeks for a
SELENA-SLEDAI score of greater than or equal to 4 and a continuation rule at 24 weeks for a SELENA-SLEDAI score of greater than or equal to 6 respectively (see section 3.48). The Committee agreed that specifying a continuation rule using an improvement in SELENA-SLEDAI score of either 4 or 6 points at 24 weeks could be considered arbitrary. On balance, it was persuaded that the application of continuation rules was appropriate, but concluded that it was not appropriate to consider using the more restrictive rule of a SELENA-SLEDAI score improvement of 6 or more as the base-case analysis for decision making.

4.18 The Committee discussed the assumption in the economic model that the effect of belimumab was maintained over time. The Committee heard from the clinical specialists that there were limited data available about the maintenance of treatment effect in systemic lupus erythematosus. Clinical specialists explained that in other conditions such as rheumatoid arthritis, patients on biological treatments can experience a reduction in the response to treatment over time. However, the clinical specialists explained that in their experience for systemic lupus erythematosus, those patients whose disease responded to rituximab and who needed retreatment with rituximab at a later stage had shown a good response to retreatment. The Committee again noted that the only longer term data submitted by the manufacturer in relation to the benefit of belimumab was the open label phase II extension study which had been reported in a conference abstract (Petri et al. 2011). The Committee concluded that there was still some uncertainty in the evidence about whether it was appropriate to assume that treatment effect was maintained over time. If the treatment effect was not maintained over time, this would lead to an increase in the ICER.
4.19 The Committee discussed the modelling of response in the economic model. The Committee noted the ERG comments that for patients receiving belimumab whose disease did not respond to treatment at 24 weeks, it was assumed that at week 52 they had the mean benefit observed in the standard care group. The ERG stated that because the standard care group included both patients whose disease had responded and not responded to standard care, this was likely to overestimate the benefit of belimumab. The ERG stated that a more appropriate approach would have been to model the changes for the group of patients whose disease did not respond to standard care. The Committee concluded that the manufacturer’s approach may have overestimated the treatment effect of belimumab.

4.20 The Committee noted that the model outputs in the original base-case analysis demonstrated a gain in survival of 2.9 years from treatment with belimumab compared with standard care. The Committee considered the predicted survival from the model, noting that there was no evidence from the trials to support this modelled outcome and that in the trials there was a trend towards higher mortality in the belimumab arms compared with standard care. The manufacturer explained that the modelled benefit was expected as a result of reduced or delayed damage to organ systems, which would in turn have an effect on mortality risk. The Committee heard from the clinical specialists that people with higher disease activity are more likely to have organ damage and die than people with lower disease activity. However, the clinical specialists stated that this was likely to be dependent on the site of organ damage. For example, treatment for people with mainly musculoskeletal or mucocutaneous damage was unlikely to result in a survival benefit. The Committee was also aware that because of the prolonged life expectancy of people treated with belimumab,
the duration of damage for the other organ systems is increased, affecting cost and health-related quality of life. The Committee also discussed how survival time in the model was predicted to be longer in the target population than in the overall trial population (31.9 years in the standard care arm of the target group compared with 30.5 years in the overall standard care arm in the overall pooled BLISS populations), even though the target population had more severe disease. The Committee noted comments from consultation that this was because of the different baseline ages of the target and trial populations. The Committee considered that while the different ages at baseline accounted for the survival difference, it noted that the age of death remained the same for both age groups. This was considered to be an unexpected finding given the longer disease history of the younger age group. The Committee concluded that although gains in survival from reduced organ damage were plausible, there was considerable uncertainty around the validity of the modelled gains in survival.

4.21 The Committee considered the standardised mortality ratios used by the manufacturer and the alternative values identified by the ERG. The Committee heard from the ERG that the values they identified were unpublished data from an English cohort of patients. The Committee heard from the clinical specialists that they considered that the standardised mortality ratios provided by the manufacturer appeared more appropriate, but highlighted in both sets the very high mortality ratios for the youngest ages (for people aged 24 years or younger). The Committee noted that the model was only modestly sensitive to the use of alternative standardised mortality ratios. The Committee concluded that it was appropriate to use the mortality ratios provided by the manufacturer in its decision making.
4.22 The Committee discussed the administration costs used in the economic model. It noted that in the original model a cost of £126 had been used, based on two hours of specialist nurse time. The Committee noted that this may be an underestimate of the costs of administration and noted that the ERG had completed a number of scenario analyses using values based on day case codes and also values used in previous appraisals of intravenous monoclonal antibodies for rheumatoid arthritis. Further, the Committee noted comments from consultation that pharmacy preparation time had not been included in the economic analyses. The Committee concluded that administration costs had been underestimated, and agreed that a value of £154 should be used as in previous appraisals of intravenous treatments of rheumatoid arthritis.

4.23 The Committee discussed the costs and utilities in the model. The Committee heard from clinical specialists that some of the costs and disutilities may not be accurately captured, specifically the difference in costs associated with renal disease (£1765 in the first year and £2453 in the second year) compared with those associated with pulmonary disease (£9679 and £9603 respectively). The Committee also noted, for example, that the disutility multiplier for the serious consequence of renal involvement was 0.97 whereas for musculoskeletal organ damage the corresponding figure was 0.67. The Committee expected that the disutility multiplier for renal involvement would be lower than 0.97. The clinical specialists further highlighted that the assumption that disutilities and costs were the same in second and subsequent years may underestimate the effects of reducing or delaying organ damage, because some types of damage such as renal damage were associated with increasing costs and reduced health-related quality of life, as damage progresses and people need
haemodialysis. The Committee concluded that deriving cost data from different sources may have led to some inconsistencies in the estimates and that the manufacturer may have underestimated some of the benefits associated with delaying certain types of organ damage.

4.24 The Committee noted that in the additional analyses provided by the manufacturer a discount rate of 1.5% for health benefits had been proposed. The Committee discussed whether this appraisal met the criteria for differential discounting of health benefits that can be applied in situations when treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years, as described in the clarification to the NICE Guide to methods of technology appraisals). The manufacturer provided a sensitivity analysis showing that the ICERs were sensitive to using discount rates of 3.5% for costs and 1.5% for benefits. The Committee considered that belimumab as it was currently modelled reflected a scenario where it was assumed there was continued treatment with continued benefit. This differed from the scenario that had led to the clarification of the methods guide, where there was limited duration of treatment with curative intent. Therefore the Committee concluded that belimumab did not meet the criteria for differential discounting of health benefits.

4.25 The Committee considered the cost effectiveness of belimumab in comparison with standard care. It discussed the ERG’s additional analyses that included an annual discontinuation rate of 13% after week 24, an administration cost of £154 and benefits and costs discounted at 3.5%. It accepted the application of the continuation rule of SELENA-SLEDAI score of greater than or equal to 4 at 24 weeks (see section 4.17), but considered that this may overestimate the proportion of patients stopping treatment if
clinicians did not stop treatment in people who were improving, but had not reached an improvement of 4 points. The Committee recognised that a scenario reflecting lifetime continuous treatment may not accurately capture how belimumab would be used in clinical practice. However, it did not consider that the proposed 6 year maximum treatment duration was sufficiently evidence-based to use as a basis for decision making. Alternative scenarios including intermittent treatment or alternative administration schedules could not be considered in the absence of any clinical and cost-effectiveness data. On this basis the Committee considered that the most plausible ICER without the patient access scheme was £61,200 per QALY gained, provided by the ERG. The Committee noted that a patient access scheme which reduced the ICER for belimumab compared with standard care had been agreed with the Department of Health. However, the Committee noted that the ICER with the patient access scheme applied remained above the threshold range usually considered as an acceptable use of NHS resources. The Committee discussed the sensitivity analyses completed by the manufacturer as well as the exploratory analyses from the ERG. The Committee considered that the revised base-case ICER with the patient access scheme presented in the additional ERG analyses was at the lower end of the likely values for the ICER given the uncertainties associated with treatment effect, estimation of the benefits over time, the linking of short-term trial outcomes to long-term data with differing study populations, validity of the modelled gains in survival, and administration costs (see sections 4.18, 4.19, 4.13, 4.20 and 4.22). The Committee concluded that, compared with standard care, belimumab could not be considered a cost-effective use of NHS resources as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high
degree of disease activity (for example, positive anti-double stranded DNA and low complement) despite standard therapy.

4.26 The Committee explored the cost-effectiveness argument for belimumab compared with rituximab. The Committee discussed the dosing of rituximab. It heard from the clinical specialists that in clinical practice, the dosing schedule for rituximab would often be lower than that described by the manufacturer. Rituximab would be prescribed as a series of two doses followed by a waiting period, rather than four doses over the course of a year. If fewer doses were prescribed, the annual cost of rituximab would be reduced below the manufacturer’s estimate of £6985. Further, the Committee noted that the costs of administration and pharmacy preparation for the treatments had not been included in the analyses, and including these would increase the costs for both drugs, but more so for belimumab because it is given every 4 weeks. It heard from the manufacturer that they considered it appropriate to compare the drug costs for both treatments as they had been used in clinical trials. Further, the shorter time for infusion of belimumab compared with the longer infusion time for rituximab offset the increased frequency of administration associated with belimumab. However, the Committee was not persuaded that the comparison of costs provided by the manufacturer accurately reflected the costs of providing rituximab and belimumab in UK clinical practice.

4.27 The Committee considered the cost effectiveness of belimumab compared with rituximab. In the absence of any formal economic modelling, the Committee considered the comparison of costs of rituximab and belimumab. The Committee had previously discussed the clinical effectiveness of rituximab in comparison with belimumab (see section 4.12) and concluded that no reliable data
were available to demonstrate the relative efficacy of belimumab in comparison with rituximab. The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. For these reasons, the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy, compared with rituximab.

4.28 The Committee discussed the innovative nature of belimumab. It specifically noted the comments from clinical specialists and patient experts that few drugs are licensed for treating systemic lupus erythematosus, and the comment from the manufacturer that belimumab was developed to target the underlying pathology of this disease. The Committee also discussed whether any health-related quality-of-life benefits may not have been captured in the calculation of the QALY. It was aware that disease flares had not been included in the economic modelling and that the manufacturer stated that this could underestimate the benefits of treatment. The Committee noted that in the BLISS trials differences in EQ-5D were demonstrated between treatment groups but that this was not statistically significant at 52 weeks. Further, there were no statistically significant differences at week 52 for FACIT-fatigue scores in the target population in people receiving belimumab compared with people receiving standard care. The Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life from belimumab had not been adequately captured. The Committee
concluded that the issues identified around innovation did not change its conclusions about the cost effectiveness of belimumab.

4.29 The Committee was aware of a potential equalities issue relating to the lower response rates observed in the clinical trials for the subgroup of patients of African American or African origin. The Committee also noted comments received during consultation that systemic lupus erythematosus predominantly affects women of child-bearing age from ethnic minority groups. Given that the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations do not limit access to the technology for any specific group, compared with other groups.
### Summary of Appraisal Committee’s key conclusions

<table>
<thead>
<tr>
<th>TAXXX</th>
<th>Appraisal title: Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key conclusion</strong></td>
<td>Belimumab is not recommended, within its licensed indication, as add-on therapy in adult with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded-DNA and low complement) despite standard therapy.</td>
<td>1.1</td>
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<tr>
<td></td>
<td>The Committee concluded that compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the most plausible ICER without the patient access scheme was £61,200 per QALY gained, provided by the ERG. The Committee noted that a patient access scheme which reduced the ICER for belimumab compared with standard care had been agreed with the Department of Health. However, the Committee noted that the ICER with the patient access scheme applied remained above the threshold range usually considered as an acceptable use of NHS resources.</td>
<td>4.10 4.25</td>
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<tr>
<td></td>
<td>There are no reliable data to show the relative efficacy of belimumab compared with rituximab. For the comparison of belimumab with rituximab the Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. Consequently, the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources, compared with rituximab.</td>
<td>4.12 4.27</td>
</tr>
<tr>
<td><strong>Current practice</strong></td>
<td>Systemic lupus erythematosus is a debilitating condition, primarily affecting younger women. It affects daily life, including the ability to work and to have children. People with systemic lupus erythematosus tend to die younger than the average population. There are very few licensed treatments for the disease and patients would welcome a new treatment option specifically for this disease.</td>
<td>4.2</td>
</tr>
</tbody>
</table>
### The technology

<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>The treatment might be steroid sparing and may reduce the side effects of other drugs, especially corticosteroids.</th>
</tr>
</thead>
<tbody>
<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
<td>Few drugs are licensed for treating systemic lupus erythematosus. Belimumab was developed to target the underlying pathology of this disease.</td>
</tr>
<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
<td>Between 10 and 15% of systemic lupus erythematosus patients have high disease activity despite standard therapy. A proportion of these are currently treated with rituximab, frequently through individual funding requests. Belimumab would be used in a similar way to rituximab.</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Adverse reactions were not a key factor in this appraisal.</td>
</tr>
</tbody>
</table>

### Evidence for clinical effectiveness

<table>
<thead>
<tr>
<th>Availability, nature and quality of evidence</th>
<th>Most of the evidence in the manufacturer’s submission was from the two BLISS trials (BLISS-52 and BLISS-76) that compared belimumab against standard care. There are no reliable data to show the relative efficacy of belimumab compared with rituximab.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance to general clinical practice in the NHS</td>
<td>The Committee concluded that although BLISS-76 was more representative of the population of England and Wales than BLISS-52, data from BLISS-52, and therefore from the pooled analysis, would be relevant.</td>
</tr>
<tr>
<td>Uncertainties generated by the evidence</td>
<td>The relevance of both the pooled and unpooled data to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, nature of standard of care and effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus.</td>
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</table>

**Table:**

<table>
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<th>Page</th>
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<td>4.2, 4.10</td>
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</tbody>
</table>
### Final appraisal determination – Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus

**Issue date:** April 2012

<table>
<thead>
<tr>
<th>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</th>
<th>The manufacturer focused on a target population who were a subgroup of the marketing authorisation population and BLISS clinical trials. The target population was identified by a SELENA-SLEDAI score of greater than or equal to 10 and evidence of serological disease activity. The Committee concluded that though specifying a SELENA-SLEDAI score of greater than or equal to 10 may be considered arbitrary, the specified target population is clinically relevant.</th>
<th>4.5</th>
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<tbody>
<tr>
<td>Estimate of the size of the clinical effectiveness including strength of supporting evidence</td>
<td>The Committee concluded that compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the evidence of effect was observed with greater consistency across outcomes in the BLISS-52 trial. Further, the relevance of both the pooled and unpooled data to a UK population was associated with a number of uncertainties in terms of the patient populations enrolled, nature of standard care and effects of belimumab on the full range of possible manifestations of systemic lupus erythematosus.</td>
<td>4.10</td>
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</table>

### Evidence for cost effectiveness

<table>
<thead>
<tr>
<th>Availability and nature of evidence</th>
<th>The manufacturer submitted an economic model in which short-term outcomes from the BLISS studies were linked to long-term outcomes, using data from the Johns Hopkins cohort.</th>
<th>4.13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainties around and plausibility of assumptions and inputs in the economic model</td>
<td>The Committee accepted that attempting to link short-term outcomes to long-term outcomes was appropriate and recognised that there were limited data sources available with which to do this. However, it concluded that there was uncertainty about whether the equations derived from the Johns Hopkins data could be reliably applied to the target population because of differences in study populations. The Committee concluded that the manufacturer may have underestimated the annual discontinuation rate in the original economic model, and therefore overestimated the ICER, and that a higher rate of annual discontinuation as observed in the phase II extension study may be more appropriate. The Committee understood that continuous treatment over many years was unlikely to reflect how belimumab would be used in clinical practice. However, the SPC for belimumab describes</td>
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continuous use as the model for administration. Although the 6 year maximum treatment duration modelled by the manufacturer in their revised analyses improved the cost effectiveness of belimumab, the rationale for the choice of 6 years could not be considered sufficiently robust for use as the basis for decision making.

There was still some uncertainty in the evidence about whether it was appropriate to assume that treatment effect was maintained over time. If treatment effect was not maintained over time, this would lead to an increase in the ICER.

Although gains in survival from reduced organ damage were plausible, there was considerable uncertainty around the validity of the modelled gains in survival.

Deriving cost data from different sources may have led to some inconsistencies in the estimates and the manufacturer may have underestimated some of the benefits associated with delaying certain types of organ damage.

| 4.18 | 4.20 | 4.23 |
| **Incorporation of health-related quality-of-life benefits and utility values** | The Committee noted that in the additional analyses provided by the manufacturer a discount rate of 1.5% for health benefits had been proposed. The Committee considered that belimumab as it was currently modelled reflected a scenario where there was continued treatment with continued benefit. This differed from the scenario that had led to the clarification of the methods guide, where there was limited duration of treatment with curative intent. Therefore the Committee concluded that belimumab did not meet the criteria for differential discounting of health benefits.  

The Committee also discussed whether any health-related quality-of-life benefits may not have been captured in the calculation of the QALY. It was aware that disease flares had not been included in the economic modelling and that the manufacturer stated that this could underestimate the benefits of treatment.  

The Committee was not persuaded that the clinical evidence submitted strongly indicated that the changes in health-related quality of life had not been adequately captured, noting in particular that FACIT-fatigue scores were not significantly better at week 52 in the target population in people receiving belimumab compared with people receiving standard care. | 4.24 |
| **Are there specific groups of people for whom the technology is particularly cost effective?** | The manufacturer focused on a target population, who were a subgroup of the population covered by the marketing authorisation and the BLISS clinical trials. The target population was identified by a SELENA-SLEDAI score of greater than or equal to 10 and evidence of serological disease activity. The ICERs for the target population were lower than those for the marketing authorisation population. | 4.5 |
| **What are the key drivers of cost effectiveness?** | The model was driven by changes in the SELENA-SLEDAI score based on data from the Johns Hopkins cohort. Cost effectiveness was not particularly driven by other factors, such as steroid use. | 4.13 |
Most likely cost-effectiveness estimate (given as an ICER)

The Committee considered that the most plausible ICER without the patient access scheme was £61,200 per QALY gained, provided by the ERG. The Committee noted that the ICER with the patient access scheme applied remained above the threshold range usually considered as an acceptable use of NHS resources.

The Committee concluded that there was no sound case presented to it on the cost effectiveness of belimumab compared with rituximab. For these reasons, the Committee did not consider that belimumab with the patient access scheme had been shown to be a cost-effective use of NHS resources as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy, compared with rituximab.

Additional factors taken into account

| Patient access schemes (PPRS) | A patient access scheme which reduced the ICER for belimumab compared with standard care has been agreed with the Department of Health. The Committee noted that the most plausible ICER provided by the ERG with the patient access scheme applied remained above the threshold range usually considered as an acceptable use of NHS resources. |
| End-of-life considerations | End-of-life considerations were not discussed. |
| Equalities considerations and social value judgements | The Committee was aware of equalities issues relating to the lower response rates observed in the clinical trials for the subgroup of patients of African American or African origin, and that systemic lupus erythematosus predominantly affects women of child-bearing age from ethnic minority groups. Given that the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations do not limit access to the technology for any specific group, compared with other groups. |
5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee acknowledged the manufacturer’s post-marketing commitment to investigate intermittent treatment with belimumab including time to flare from withdrawal of treatment and response to
belimumab at retreatment, and considered that these studies would be of value.

7 Related NICE guidance

There is no related guidance for this technology.

8 Review of guidance

8.1 The guidance on this technology will be considered for review in August 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Clark
Chair, Appraisal Committee
April 2012
Appendix A: Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Professor Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Professor Jonathan Michaels (Vice Chair)
Professor of Clinical Decision Science, University of Sheffield

Professor Darren Ashcroft
Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor Usha Chakravarthy
Professor of Ophthalmology and Vision Sciences, The Queen’s University of Belfast

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester
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Professor Femi Oyebode  
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford  
Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge  
GP and Consultant in Medicines Management, NHS Lothian

Cliff Snelling  
Lay member

Dr Brian Shine  
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray D Smith  
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie  
Lay Member

Charles Waddicor  
Chief Executive, NHS Berkshire

C NICE project team

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

Dr Helen Starkie and Richard Diaz  
Technical Lead(s)

Zoe Garrett  
Technical Adviser

Kate Moore  
Project Manager
Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:


B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- GlaxoSmithKline

II Professional/specialist and patient/carer groups:

- Lupus UK
- National Kidney Federation
- British Association of Dermatologists
- British Health Professionals In Rheumatology
- British Renal Society
- British Society for Rheumatology
- Primary Care Rheumatology Society
- Renal Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Bolton Primary Care Trust

National Institute for Health and Clinical Excellence
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Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety, Northern Ireland
- Healthcare Improvement Scotland
- Arthritis Research UK
- Cochrane Skin Group
- Kidney Research UK
- National Institute for Health Research Health Technology Assessment Programme
- Warwick Evidence

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on belimumab by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor David Isenberg, Academic Director of Rheumatology, University College London, nominated by British Society for Rheumatology – clinical specialist
- Dr Liz Lightstone, Consultant Renal Physician, nominated by Renal Association – clinical specialist
- Jane Dunnage, Chair and Trustee of Lupus UK, nominated by Lupus UK – patient expert
- Chris Maker, Director of Lupus UK, nominated by Lupus UK – patient expert
D The following individuals were nominated as NHS Commissioning experts by the selected PCT allocated to this appraisal. They gave their expert/NHS commissioning personal view on belimumab by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Johanna Taylor, Clinical Effectiveness Pharmacist, Bolton Primary Care Trust, selected by Bolton Primary Care Trust – NHS Commissioning expert

E Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- GlaxoSmithKline