NICE Belimumab response

**A) Has all the relevant evidence been taken into account?**
As far as we were aware, although reference is made to ERG’s consideration of an unpublished trial in para 3.38

**B) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
1) the results from 2 clinical trials were submitted, BLISS 52 and BLISS 76: the primary outcome was statistically significant in both trials (3.7). BLISS 76 showed a statistically significant difference in response rate between belimumab and standard care (3.7). We therefore find it difficult to know how the committee can reject the findings of the BLISS 76 trial.

2) the results from BLISS 52 trial (which gives clearer evidence of effect) was not considered so seriously by the committee because of the racial mix not being seen as generalisable to this country’s population (3.28, 3.5). We did point out during the meeting that SLE affects all races, but is disproportionately higher and often more serious in certain racial groups; we also pointed out that the racial mix of the UK is now very diverse and wide, for example there is a large Asian population in many large cities in this country (4.6).

The committee’s consideration of the clinical evidence (4.6-4.10) seems to waver between acknowledging that BLISS 52 population may have some relevance to UK (4.6: ‘pooled analysis could be considered relevant’) and dismissing it (4.9: ‘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 SLE’). Whilst accepting that the numbers in each study, when pooled, give a greater weight to the findings of BLISS 52 as the sample size was bigger, we feel that more consideration of data from BLISS 52 should be given by the committee in reaching their decision.

3) Evidence for secondary outcomes may not be so clear: lupus patients can have a multiplicity of symptoms (and their often fluctuating or flitting pattern) which make it very difficult for precise endpoints to be observed. For some patients improvement would be outside the remit of the specified secondary outcome measures, but could have given a positive effect during the trials.

There was evidence of a reduction in steroid use, although this may have been insufficient to avoid side effects, lupus patients are always grateful for anything which reduces the need for steroids. It is a great milestone to come off steroids altogether, which unfortunately is very difficult for many people to pass, so any treatment which has some effect would be extremely welcome and a real boost to morale for those where other treatments have not managed to reduce the burden of steroids.

Trials were conducted on patients with a high level of disease activity (score of 10+ SLEDAl) (3.1, 4.4), mainly mucocutaneous, immunological and/or musculoskeletal damage (3.5). These systems may also not give such clear markers of improvement and be open to fluctuation.

Unlike many drug trials where subjects receive either drug or placebo, standard care was continued for all patients in the trials, therefore a clear improvement between those receiving the drug and those on placebo would be less easily observed.

4) some results from BLISS 76 showed improvements early (some at week 24, many at week 52): this seems to have been taken by the committee as evidence that the 76 week trial was less effective,
but this may be indicating that the drug has effect in a shorter period of time than 76 weeks. This information should not lead to dismissing its effectiveness as paras 2.3 and 3.32 states that the drug will be discontinued at 6 months if there is no improvement. This may have a bearing on the length of time the drug would need to be used and therefore the costings.

C) Are the provisional recommendations sound and a suitable basis for guidance in the NHS?
1) Rituximab is given as a comparator within the appraisal document, but 3.13 notes that ‘the EXPLORER trial showed no statistically significant differences in major or partial clinical responses between the rituximab group and the placebo group over 52 weeks’. In fact belimumab did meet its primary endpoint and showed some improvement in other symptoms: this would appear to be better ‘evidence’ for belimumab than for rituximab.

2) What guidance is NICE giving to both lupus patients and their clinicians? It would appear that rituximab is preferred to belimumab by the Appraisal committee for lupus patients, but trials of rituximab were not conducted on lupus patients, so we are left with unclear guidance on prescribing, especially for patients where existing therapies have not been effective and the activity of the disease is out of control and likely to result in either very serious organ damage or death, not allowing time for special application to be made to local trusts for decision.

D) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?
1) We stated that SLE affects many racial groups more severely than the Caucasian population. Many drug trials are conducted on white male populations: in the BLISS 52 trials we see that belimumab was shown to have better effect on certain racial populations, but the committee thought that this population was not generalisable to the UK population: we feel that this decision will disadvantage certain racial groups where the drug has been seen to be effective.

2) If NICE does not give clear guidance on funding for this drug, we feel that will disadvantage certain racial groups, where English may not be their first language, and they may not have the experience or confidence to challenge decisions made locally.

LUPUS UK
21st October 2011