Health Technology Appraisal

Abatacept for the treatment of Rheumatoid Arthritis after the failure of conventional disease-modifying anti-rheumatic drugs.

Pfizer response to the abatacept ACD and evaluation report

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Pfizer welcomes the opportunity to comment on the ACD and the evaluation report of abatacept for the treatment of Rheumatoid Arthritis (RA) after the failure of conventional disease-modifying anti-rheumatic drugs (DMARDs). Overall we agree that the provisional recommendations for abatacept for this indication are sound and are a suitable basis for guidance to the NHS.

We note from the ACD that there are 3 potential decision populations that have been included in this appraisal:

1. The population originally specified in the NICE scope for this appraisal, which specified abatacept should be compared with other biological DMARDs or conventional DMARDs in people with moderate and severe active RA who had responded inadequately to previous therapy with one or more conventional including methotrexate (MTX).

2. The manufacturer, then, specifically focused their submission of abatacept in comparison with infliximab in a subpopulation of people who may not be able to use subcutaneous therapies.

3. An additional decision problem was posed by clinical experts which compares abatacept with conventional DMARDs, but only in a subpopulation of people for whom clinicians consider TNF inhibitor treatment inappropriate because of a contraindication.

Accordingly, we believe that etanercept should only be considered as a comparator to abatacept if the original scoping population remains applicable. If this is the case, then, our specific concern about the appraisal is the inclusion of the TEMPO trial in the manufacturer's mixed treatment comparison (MTC) and the use of the current MTC results in the economic model.

In addition, we have identified a number of issues/errors in our review of the evaluation report and these are summarised in appendix 1 of our response.

- **The inclusion of the etanercept TEMPO (Klareskog et al 2004) trial in the basecase MTC analysis**

Pfizer notes that the manufacturer acknowledges in 5.7.1 of their submission document that TEMPO 'may have included a different study population to the other studies, as the patient population included was not composed of inadequate responders to methotrexate, but to conventional DMARDs.' We would argue that TEMPO is fundamentally different from all the comparator biologic DMARD trials in this analysis since patients did not need to have demonstrated an inadequate response to MTX at baseline. These participants were more likely to benefit from MTX and as a

result the observed placebo response reported in this trial was higher than in other biological DMARD trials. Pfizer would recommend that that TEMPO should be excluded from the abatacept MTC, as it also does not meet the population of interest specified in the NICE scope, which is 'adults with RA who have had an inadequate response to one of more conventional DMARDs including MTX.'

Furthermore, NICE in previous published appraisals for RA treatment tocilizumab (TA198) and certolizumab pegol (TA186) and the NICE ACD for golimumab after failure of previous anti-rheumatic drugs has noted that the TEMPO trial was different from other biologic DMARD trials because of the unusually high placebo response rate. NICE has previously requested that it should be excluded from the analysis. Therefore, to be consistent with previous NICE appraisals this trial needs to be removed from the analysis or a scenario analysis conducted with it removed.

Appendix 1 – Errors/issues presented in the evaluation report

Study/Studies/issues	Comment
RAPID 1 and RAPID 2	We would like to highlight that the efficacy estimates of certolizumab pegol with MTX in the MTC may lead to an overestimation of its benefit and these should be treated with caution due to the uncertainty around its true benefit. • Patients were excluded 8 weeks before the primary efficacy endpoint and treated as non responders. However in these 8 weeks it is possible that some patients would have achieved an ACR20 response and were incorrectly assumed to have a no response. This is likely to affect the control arm to a greater extent due to the higher withdrawal rate (63-81%) compared to the intervention arms (17-21%). • It has been shown that methotrexate is most effective when step-up therapy is employed (as it is in the majority of other trials). The restriction on dose increases may have resulted in patients being taken into rescue therapy from the control arm that would have responded by week 24. This would result in a greater difference between certolizumab pegol efficacy and that seen in the control arm.
ATTRACT	The primary end point for ATTRACT trial is at 30 weeks for ACR20, but the inclusion criteria that the manufacturer has used for ACR response is 24/28 weeks. This trial therefore falls outside the inclusion criteria of the analysis and thus we

	question its inclusion.
Assuming the same time on treatment for all the biologics in the abtacept economic model	There is evidence from European registries and observational data that suggests that the time on treatment for biologic DMARDs (predominantly adalimumab, etanercept and infliximab) is not the same, for example, in the Danish DANBIO, Swedish SSATG and Italian Lorhen registries. We note that the manufacturer assumed the same time on treatment for all biologics. We argue that this fails to address the evidence and accordingly the uncertainty that time on treatment for biologic DMARDs may not be the same.
The use of HAQ instead of ACR response as the initial response to biologic therapy in the abatacept economic model	We understand the manufacturer's rationale for using HAQ as the initial response to biologic therapy in the economic model given the limited availability of DAS 28 outcomes reported in randomised clinical trials (RCTs). However, we would argue that ACR response should also be considered in the economic model because: • There are a similar number of RCTs that report ACR, when compared to the number reporting HAQ, in the manufacturer literature search for the MTC. The evidence base is therefore similarly strong for both disease specific measures. ACR is, also the primary endpoint in the majority of trials. • The use of ACR, as an initial response has been used in a number of previous recent NICE appraisals in RA, notably certolizumab pegol, tocilizumab and golimumab. We suggest that to allow comparison between different NICE appraisals there needs to be consistency in the evidence appraised. We acknowledge that using ACR instead of HAQ leads to additional uncertainty through mapping between the disease specific measures. But, a more appropriate approach, we would argue is to try both HAQ and ACR response separately as the initial response to treatment, in order, to fully explore the sensitivity of initial efficacy estimates on the abatacept economic model's results.