

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final appraisal determination

### Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs

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

## 1 Guidance

- 1.1 Abatacept in combination with methotrexate is not recommended for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has responded inadequately to one or more conventional non-biological disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate.
- 1.2 People currently receiving abatacept in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has responded inadequately to one or more conventional non-biological DMARDs including methotrexate should have the option to continue treatment until they, and their clinicians, consider it appropriate to stop.

## 2 The technology

- 2.1 Abatacept (Orencia, Bristol-Myers Squibb) is a selective T-cell modulator that blocks a co-stimulatory signal required to activate T-cells. Abatacept has a marketing authorisation for use in

combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has responded inadequately to previous therapy with one or more DMARDs including methotrexate or a tumour necrosis factor (TNF) inhibitor.

- 2.2 Common adverse effects of abatacept therapy include infections, sepsis and pneumonia. Abatacept is contraindicated in people with severe, uncontrolled or opportunistic infections. Before initiating therapy, clinicians should evaluate people for both active and inactive (latent) tuberculosis infection. For full details of adverse effects and contraindications, see the summary of product characteristics (SPC).
- 2.3 Abatacept is administered as a 30-minute intravenous infusion. After an initial infusion (week 0), a person receives an infusion at week 2, at week 4 and every 4 weeks thereafter. Abatacept is available in 250-mg vials at a cost of £242.17 per vial (excluding VAT; 'British national formulary' [BNF] edition 61). Fourteen infusions are required in the first year, and 13 infusions in subsequent years. The dose of abatacept depends on body weight: people weighing less than 60 kg, 60–100 kg and over 100 kg require 500 mg, 750 mg and 1000 mg respectively. The annual drug costs associated with abatacept vary according to body weight and the number of infusions required. For a person weighing 60–100 kg, the cost is £10,171.14 in the first year, and £9444.63 in subsequent years. Costs may vary in different settings because of negotiated procurement discounts.

### 3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of abatacept and a review of this submission by the Evidence Review Group (ERG; appendix B).

#### *Clinical effectiveness*

- 3.1 The decision problem defined in the scope asked whether abatacept plus methotrexate is clinically and cost effective in adults whose disease has not responded adequately to one or more conventional DMARDs, including methotrexate, compared with conventional non-biological DMARDs (from now on referred to as conventional DMARDs) or compared with biological DMARDs. (Biological DMARDs are recommended in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' [NICE technology appraisal guidance 130; TA130] and 'Certolizumab pegol for the treatment of rheumatoid arthritis' [NICE technology appraisal guidance 186; TA186]),. The manufacturer addressed this decision problem, but in addition, focussed its submission specifically on a population of people for whom self-administration of subcutaneously-injected biological DMARDs is unsuitable. The manufacturer stated that this would include people with problems handling the injection devices, people with mental health problems, or with an aversion to, or phobia of, needles. The manufacturer estimated that approximately 10% of people eligible for a biological DMARD would not be able to self-inject subcutaneously. Of the biological DMARDs recommended by NICE as treatment options after an inadequate response to conventional DMARDs, only infliximab is administered intravenously. Therefore, the manufacturer focussed on two comparators for abatacept plus

methotrexate: infliximab plus methotrexate, and conventional DMARDs, which have not yet been tried in the treatment pathway.

3.2 To establish the efficacy of abatacept plus methotrexate compared with infliximab plus methotrexate, the manufacturer performed a systematic review to identify randomised controlled trials (RCTs) comparing abatacept plus methotrexate with infliximab plus methotrexate, or placebo plus methotrexate. The manufacturer sought head-to-head trials to provide direct evidence, and placebo-controlled trials to provide indirect evidence. The manufacturer identified four RCTs; of these one compared 2 mg/kg or 10 mg/kg abatacept plus methotrexate with placebo plus methotrexate (Kremer phase 2b [n = 339]), two compared 10 mg/kg abatacept plus methotrexate with placebo plus methotrexate (AIM [n = 652] and IM101-119 [n = 50]), and one compared abatacept 10 mg/kg plus methotrexate with infliximab 3 mg/kg plus methotrexate or placebo plus methotrexate (ATTEST [n = 431]). Three trials lasted 1 year (the Kremer phase 2b, AIM and ATTEST trials). The AIM and ATTEST trials enrolled people who had active rheumatoid arthritis for at least 1 year, and the IM101-119 trial lasted 4 months and enrolled people who had active rheumatoid arthritis according to disease activity score 28 (see section 3.3). The Kremer phase 2b trial enrolled people who had active rheumatoid arthritis, but the duration of their disease was not stated. The average number of DMARDs previously received by the trial participants ranged from 1.2 to 1.8 (reported in AIM and ATTEST trials). The mean time since first diagnosis was approximately 2.3 years in the IM101-119 trial and between 7.3 and 9.7 years in the three other trials.

3.3 Several tools were used to assess the response to treatment in rheumatoid arthritis. The Stanford Health Assessment

Questionnaire (HAQ) and the shorter HAQ-Disability Index (HAQ-DI) or Modified Health Assessment Questionnaire (M-HAQ) score the ability to perform daily activities; ranging from 0 (least disability) to 3 (most severe disability). The American College of Rheumatology (ACR) response criteria (ACR20, ACR50 and ACR70) require improvement in a percentage (20, 50 or 70% respectively) of tender joints, swollen joints, global assessments, pain, disability and circulating inflammatory markers. The disease activity score (DAS) is calculated using a formula that includes counts for tender and swollen joints (53 and 44 joints respectively), an evaluation of general health (on a scale of 0 to 100) and a measure of circulating inflammatory markers. DAS28 is similar to DAS, but assesses 28 joints only. A DAS28 score greater than 5.1 indicates high disease activity, between 3.2 and 5.1 moderate disease activity, less than 3.2 low disease activity, and a score of less than 2.6 indicates remission. An improvement in DAS28 score of 0.6 or less indicates a poor response, and an improvement greater than 1.2 indicates a good response.

- 3.4 Primary outcomes differed by study. The AIM and Kremer phase 2b trials measured ACR20 at 6 months. The AIM trial also measured change from baseline in radiographic progression of joint erosions and of physical function of at least 0.3 in HAQ-DI at 1 year as primary outcomes. DAS28 at 6 months was the primary endpoint in the ATTEST study, while change in wrist synovitis score at 4 months was the primary outcome measure in study IM101-119. Secondary outcomes in the trials included: physical function measured using either the HAQ-DI or M-HAQ (referred to from now on as HAQ), ACR response, health-related quality of life as measured by the short-form 36 (SF-36) questionnaire, global assessment scales and adverse events.

- 3.5 At 6 months, three of four trials reported statistically significant differences in mean improvements in HAQ score, ranging from -0.19 to -0.38 with abatacept plus methotrexate compared with placebo plus methotrexate. At 1 year, two trials reported statistically significant differences in mean improvements in HAQ score of -0.29 ( $p < 0.001$ ) and -0.36 ( $p < 0.001$ ) compared with placebo plus methotrexate.
- 3.6 At 6 months and 1 year, the three trials reported a higher likelihood of achieving a clinically meaningful improvement in physical function (defined as a reduction in HAQ score of 0.22 in the Kremer phase 2b study, and of 0.3 in the AIM and ATTEST trials) with abatacept plus methotrexate compared with placebo plus methotrexate. The relative risks for a clinically meaningful improvement in physical function at 6 months with abatacept plus methotrexate compared with placebo plus methotrexate in the individual trials were 1.34 (95% confidence interval [CI] 1.14 to 1.58), 1.73 (95% CI 1.29 to 2.33) and 1.50 (95% CI 1.16 to 1.94) and at 1 year were 1.61 (95% CI 1.35 to 1.94) and 1.79 (95% CI 1.27 to 2.52).
- 3.7 At 6 months and 1 year, abatacept plus methotrexate led to significantly higher probability of having low disease activity and of achieving remission than placebo plus methotrexate as measured by DAS28 relative to baseline. The ATTEST study, which was not adequately powered to detect differences between abatacept and infliximab, reported non-significant mean improvements in DAS28 score at 6 months (-0.28) and at 1 year (-0.62) with abatacept plus methotrexate compared with infliximab plus methotrexate. The ATTEST study also reported that abatacept plus methotrexate was associated with a significantly higher probability of having low

disease activity at 6 months and 1 year, and a higher likelihood of remission at 6 months and 1 year than infliximab plus methotrexate.

- 3.8 The outcome of ACR responses at 6 months and/or 1 year were reported in all three 1-year trials as a primary or secondary outcome. At both 6 months and 1 year, abatacept 10 mg/kg and infliximab were associated with a significantly higher probability of achieving an ACR20, ACR50 or ACR70 response than placebo. There were no reported statistically significant differences between the groups randomised to abatacept or infliximab in ACR20, ACR50 or ACR70 at 6 months or 1 year.
- 3.9 The AIM, ATTEST and Kremer phase 2b trials measured health-related quality of life using the SF-36 questionnaire at baseline, 6 months and 1 year. Quality of life data were not collected in the IM101-119 trial. None of the trials collected health-related quality of life data using the EuroQol 5-D (EQ-5D) questionnaire. In the Kremer phase 2b and AIM trials, abatacept plus methotrexate led to statistically significant improvements from baseline in the physical and mental components of the SF-36 at 6 months compared with placebo plus methotrexate. The ATTEST study reported significant improvements in the physical and mental components of the SF-36 in both the groups randomised to abatacept and to infliximab compared with placebo.
- 3.10 The manufacturer presented data on adverse events from the ATTEST, Kremer phase 2b, AIM and IM101-119 trials. In the three 1-year trials, abatacept was not associated with a significantly higher rate of serious adverse events compared with placebo at 6 months or 1 year. The ATTEST study reported that abatacept plus methotrexate compared with infliximab plus methotrexate was

associated with lower rates of serious adverse events at 1 year (9.6% versus 18.2%), lower rates of discontinuing the drug because of adverse events (3.2% versus 7.3%), lower rates of discontinuing the drug because of serious adverse events (2.6% versus 3.6%), lower rates of serious infections (1.9% versus 8.5%) and acute infusion events (7.1% versus 24.8%). Longer term data incorporated into the safety analyses of abatacept indicated that the incidence of serious adverse events did not increase over time.

- 3.11 To compare the efficacy of abatacept plus methotrexate with placebo plus methotrexate, the manufacturer carried out a series of pairwise meta-analyses using data from the Kremer phase 2b, AIM and ATTEST trials. The manufacturer's fixed effects meta-analyses reported a mean reduction (improvement) from baseline in HAQ score for abatacept plus methotrexate compared with placebo plus methotrexate at 24 or 26 weeks ( $-0.2524$ , 95% CI  $-0.3253$  to  $-0.1794$ ) and 52 weeks ( $-0.3105$ , 95% CI  $-0.3934$  to  $-0.2275$ ). A mean reduction (improvement) from baseline in DAS28 score was reported for abatacept plus methotrexate compared with placebo plus methotrexate at 24 or 28 weeks ( $-1.123$ , 95% CI  $-1.3275$  to  $-0.9186$ ).
- 3.12 The manufacturer's systematic review also identified trials for a mixed treatment comparison intended to compare abatacept plus methotrexate with five biological DMARDs, all plus methotrexate (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), and with placebo plus methotrexate. The mixed treatment comparison included 11 trials, and focussed on the change in the HAQ score from baseline to 24 or 26 weeks. The absolute change from baseline for biological agents plus methotrexate was  $-0.46$  for infliximab,  $-0.55$  for etanercept,  $-0.57$

for abatacept, -0.60 for adalimumab, -0.61 for golimumab and -0.65 for certolizumab pegol. The absolute change from baseline for placebo plus methotrexate was -0.27. The mixed treatment comparison showed that abatacept plus methotrexate showed efficacy comparable with that of most other biological DMARDs. The mixed treatment comparison also reported the mean rate of serious adverse events for the interventions from the included trials. The average percentage of people discontinuing treatment because of serious adverse events ranged from 0.0% for palliative care to 12.8% for certolizumab pegol.

### ***Cost effectiveness***

- 3.13 The manufacturer systematically reviewed economic evaluations of abatacept plus methotrexate for people with moderate to severe active rheumatoid arthritis whose disease had not responded adequately to methotrexate monotherapy, or who were intolerant to methotrexate monotherapy. Fourteen economic evaluations met the inclusion criteria for the systematic review. However, the manufacturer considered that none addressed the decision problem for this appraisal.
- 3.14 The manufacturer developed a new economic model that was based on cost-utility analyses run over a lifetime horizon and from the perspective of the healthcare provider. The model addressed the cost effectiveness of abatacept compared with three comparators: all other biological DMARDs, conventional DMARDs and infliximab plus methotrexate. Infliximab, like abatacept, is administered intravenously, and is the only intravenously administered biological DMARD recommended by NICE at this point in the clinical pathway for the treatment of rheumatoid arthritis. All people entering the model are assumed to either have

severe active rheumatoid arthritis that has responded inadequately, or to have intolerance to methotrexate and also possibly to other conventional DMARDs, but not to a biological DMARD.

- 3.15 The model begins with the person entering an initial treatment phase and receiving treatment with abatacept plus methotrexate, or a different biological DMARD plus methotrexate (that is, adalimumab, certolizumab pegol, etanercept, golimumab or infliximab), or a conventional DMARD. The model assumes that people receive this initial treatment for 6 months unless their rheumatoid arthritis did not respond (defined as a HAQ change from baseline of less than 0.3), they experienced a serious adverse event, or they died. The model assumes that people whose disease responded did not have an adverse event, or people who did not die remained on their allocated treatment and entered a long-term maintenance phase. As modelled, people leave this long-term phase if the treatment becomes ineffective (if there is no longer a HAQ reduction of 0.3) or if they die. People who discontinue their allocated treatment either in the initial phase or the long-term phase, regardless of their initial treatment, enter the next phase of treatment with a sequence of conventional DMARDs (leflunomide, gold, azathioprine, ciclosporin, penicillamine), and then palliative care. The sequence continues until the person dies.
- 3.16 The simulated cohort of people in the model had a mean age of 51.5 years with a standard deviation of 12.90; 77.8% were women. The simulated cohort had a mean baseline HAQ of 1.71 with a standard deviation of 0.70.
- 3.17 The model assumed that a person receiving a particular drug could experience serious adverse events and that these occur only within the first 6 months of treatment (during the initial treatment phases).

The manufacturer obtained the rates for serious adverse events for each treatment from its mixed treatment comparison. The model assumed that if a serious adverse event did occur, the person discontinued treatment and their HAQ score returned to the value at which they began treatment. The manufacturer did not model any costs or decreases in utility associated with experiencing an adverse event.

- 3.18 The manufacturer assumed that during the initial 6-month treatment phase, a person continued treatment if their HAQ score dropped (improved) by at least 0.3 from baseline. The figure of 0.3 was derived by the manufacturer from the AIM and ATTEST trials. The manufacturer estimated how much a person's disease would improve with a given drug, using the HAQ changes from the mixed treatment comparison. The manufacturer assumed that all changes in HAQ would occur gradually and increase over 3 months, at which point the HAQ score would reflect all the possible improvement. If the person's HAQ scores did not improve by 0.3, the person discontinued treatment and the manufacturer assumed that their HAQ score returned (rebounded) immediately to the value at which their treatment began. For people who continued into the maintenance phase, the manufacturer assumed that people on a given biological DMARD were no more or less likely to discontinue the drug. The manufacturer estimated the time to discontinuing a biological DMARD from a Weibull distribution, with a mean value of 8.82 years and median value of 4.21 years.
- 3.19 The economic model assumed that while people receive biological DMARDs, after initially improving over 3 months, their HAQ score remains constant. The model also assumes that while people receive conventional DMARDs, their HAQ score increases

(worsens) by 0.045 each year, or while people receive palliative care, their HAQ score increases by 0.06 each year. Therefore, the HAQ scores of people who receive biological DMARDs would be the same at the end of treatment as at the start of treatment; while the HAQ scores of people who received conventional DMARDs and palliative care would be higher. The manufacturer assumed that the worse the HAQ score, the greater the risk of death, and that a person could die at any phase of the model. The manufacturer assumed that the magnitude of this increase (relative risk) was 1.33 (95% CI 1.10 to 1.61) for each unit increase in HAQ score. The manufacturer derived this estimate from a North American paper published in 1994 by Wolfe et al.

- 3.20 The manufacturer used 2009 costs in the model, which were taken from UK sources and publications identified in the systematic review. The manufacturer took the costs associated with biological DMARDs from the BNF 60. The manufacturer did not give separate costs for either conventional DMARDs or palliative care, but rather incorporated these into the costs associated with the disease (see below). The manufacturer defined the dosage of the biological DMARDs in accordance with each drug's SPC. The manufacturer assumed that a person received abatacept infusions at the start of treatment, 15 days later, 29 days later, and thereafter every 4 weeks. The dose of abatacept depended on the person's weight: people who weighed less than 60 kg received two vials (£484.34), people who weighed between 60 kg and 100 kg received three vials (£726.51) and people who weighed over 100 kg received four vials (£968.68). The manufacturer did not assume in the base-case scenario that people could share a vial of abatacept. The manufacturer assumed that the doses of either infliximab or etanercept could increase over time: 29% of people receiving

infliximab had their dose increased to 5 mg/kg at 1 year and 1% of people receiving etanercept had their dose increased to 37.5 mg at 1 year. In contrast to this, the manufacturer assumed that people receiving abatacept would not require higher doses over time. The manufacturer incorporated costs associated with rheumatoid arthritis into the model by relating a cost to an interval in the HAQ score. For example, a HAQ score less than 0.6 was associated with a cost of £2733 and a HAQ score between 0.6 and less than 1.1 was associated with a cost of £3668. These costs included hospitalisation, surgical interventions, ambulatory and community care, monitoring, conventional DMARDs and palliative care.

- 3.21 The manufacturer assumed that utility values applied in the model were dependent on HAQ score. The higher (worse) the HAQ score, the lower the utility. In the base case, the manufacturer used a quadratic (a non-linear) equation to map HAQ score to utility. The manufacturer stated that in a previous NICE technology appraisal ('Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' [NICE technology appraisal guidance 195]) the manufacturers and the assessment group mapped utility values from the HAQ score.
- 3.22 The manufacturer presented pairwise and fully incremental results. The manufacturer presented deterministic base-case results in two ways: firstly, comparing abatacept plus methotrexate with all treatments (including other biological DMARDs and conventional DMARDs) and secondly, by comparing abatacept plus methotrexate with infliximab and conventional DMARDs. When the manufacturer presented results for abatacept compared with all treatments, abatacept was dominated by adalimumab and

certolizumab pegol (that is, abatacept was less effective but cost more than adalimumab and certolizumab pegol). When abatacept, infliximab and conventional DMARDs were compared (assuming that some people could not receive subcutaneous interventions), then infliximab was extendedly dominated (that is, a combination of abatacept and conventional DMARDs would provide the same health gain as for infliximab, but at a reduced cost). There were 6.16 quality-adjusted life years (QALYs) gained with abatacept plus methotrexate compared with 4.88 QALYs gained with conventional DMARDs. Total costs were £114,548 with abatacept plus methotrexate and £76,276 with conventional DMARDs. The manufacturer estimated the incremental cost-effectiveness ratio (ICER) to be £29,916 per QALY gained for abatacept plus methotrexate compared with conventional DMARDs.

- 3.23 The manufacturer conducted a range of one-way sensitivity analyses to test whether the changes in values within the model materially changed the ICER. Reducing the time horizon to 5 years had the greatest effect on the ICER, which increased to £84,390 per QALY gained for abatacept plus methotrexate compared with conventional DMARDs. Changes that had a small effect on the ICER included using a linear rather than a non-linear function to map HAQ to utility, and changing the decrease in HAQ that defined whether a person had responded to a drug.

### ***Comments from the Evidence Review Group (ERG)***

- 3.24 The ERG noted that the manufacturer's evidence base for assessing clinical effectiveness may not be complete because the manufacturer's Medline search strategy failed to identify at least one relevant publication, excluded relevant databases and was restricted to trials published in English.

- 3.25 The ERG stated that the manufacturer presented the results of the trials inconsistently and with omissions, and did not present all the relevant data available in the public domain. The ERG commented that the manufacturer did not always provide an explanation when it presented data in its submission that differed from published data.
- 3.26 The ERG noted that people in the included trials had not had rheumatoid arthritis for as many years, or had taken as many conventional DMARDs as people in UK clinical practice starting a biological DMARD. Therefore, although the evidence submitted largely reflected the decision problem defined in the scope, the ERG considered that the difference between the populations may translate to a smaller actual benefit from abatacept in UK clinical practice than was observed in the trial populations. This was because people with disease of longer duration or who have received a larger number of treatments may not respond as well as people with disease of shorter duration or who have received fewer treatments.
- 3.27 The ERG considered that the included trials were of reasonable methodological quality. However, the ERG noted that the Kremer phase 2b may have been biased, because the discontinuation rates differed in people randomised to placebo and active treatment. The AIM trial may also have been biased because people who did not adhere to treatment were excluded. In addition, the ERG noted that no efficacy data were available relating to the extra-articular manifestations of disease, and data relating to some outcomes that are important to people with rheumatoid arthritis (pain, fatigue, sleep quality, and health-related quality of life) were poorly presented.

- 3.28 The ERG undertook its own meta-analyses to compare the efficacy of abatacept plus methotrexate with placebo plus methotrexate based on relative risk. The analyses confirmed the overall results from the trials identified by the manufacturer.
- 3.29 The ERG considered that the manufacturer's economic model was relatively complex in its programming. The ERG noted a number of concerns including: the model structure; the population of the model; the internal validity of the model; and the probabilistic sensitivity analyses.
- 3.30 Regarding the model structure, the ERG considered that the design did not reflect current clinical practice in the UK. For example, the model does not allow use of multiple biological DMARDs (that is, a person receives only one biological DMARD and if discontinued, conventional DMARDs are restarted), which is not in line with NICE guidance. The ERG stated that a comparison of abatacept compared with sequences of drugs including multiple biological DMARDs would not favour abatacept.
- 3.31 The HAQ score was used by the manufacturer to determine a number of factors throughout the model including utility, costs, whether a treatment continues, and the risk of dying. However, the ERG noted that DAS28, rather than the HAQ score, is routinely used in clinical practice and is likely to be more useful. The ERG noted that a sufficient response in the model for a person to continue treatment was a change in HAQ score of at least 0.3 from baseline. The ERG highlighted that although this was based on the endpoints of the key trials, the confidence intervals are such that an improvement of 0.3 in HAQ score may not be statistically significant. This means that the model does not account for the

possibility that a person's rheumatoid arthritis could worsen despite receiving biological DMARDs.

- 3.32 The ERG was concerned that the probabilistic sensitivity analysis did not include any variation around HAQ score. The ERG stated that this resulted in the confidence interval for the mean probabilistic ICERs being smaller than would be expected, and that the results from the manufacturer were therefore incorrect.
- 3.33 The ERG stated that a random effects meta-analysis of serious adverse events, rather than the fixed effects meta-analysis used by the manufacturer, would have been more appropriate, because it quantifies the degree of heterogeneity between trials. The ERG was aware that the manufacturer incorporated no costs or decreases in utility into the model when people experienced serious adverse events. The ERG considered that including these could reduce the ICERs for abatacept compared with infliximab, because people on abatacept experience fewer serious adverse events than people on infliximab. In addition, the ERG was unclear what impact omitting non-serious adverse events from the model might have on the ICERs. The manufacturer's model did not include any decrease in utility for people receiving an intravenous infusion; the ERG considered that because people receive abatacept more often than infliximab, then this could potentially increase the ICERs for abatacept relative to infliximab.
- 3.34 The ERG considered that in using the HAQ score, the manufacturer approximated the costs associated with rheumatoid arthritis appropriately. However, the ERG was concerned that the actual costs chosen by the manufacturer may have included costs associated with decreased productivity from a person's reduced ability to work, and as such would fall outside the NICE reference

case, which includes only costs to the NHS and carers. The ERG considered that more appropriate costs would be £1120 per HAQ unit, which was used in TA195.

3.35 The ERG undertook exploratory univariate sensitivity analyses to investigate the impact of some of the key assumptions on the cost-effectiveness estimates for abatacept. The exploratory analyses focussed on comparing abatacept with infliximab and conventional DMARDs in people for whom subcutaneous injections may be inappropriate. The exploratory sensitivity analysis showed that the ICER for abatacept plus methotrexate varied from £28,464 to £32,077 per QALY gained compared with conventional DMARDs, and £29,322 to £53,534 per QALY gained compared with infliximab plus methotrexate. The key parameter affecting the ICER for abatacept plus methotrexate compared with conventional DMARDs was reducing the time horizon to 5 years. The key parameters affecting the ICER for abatacept plus methotrexate compared with infliximab were whether vial sharing or dose escalation were assumed.

3.36 The ERG undertook multivariate scenario analyses as follows:

- Objective analysis: The ERG corrected arithmetic errors in the manufacturer's submission; applied costs of £1120 for each unit of HAQ that excluded losses in productivity associated with rheumatoid arthritis (instead of different costs for every half interval of HAQ change as was assumed by the manufacturer); sampled the time to discontinuing infliximab and abatacept independently (instead of dependently); set the standard deviation of response to treatment to 0.3; set the rates of serious adverse events as equal for abatacept and infliximab; and excluded the possibility of escalating the dose of infliximab.

- Favourable analysis: The ERG used its objective analysis but also took the rate of serious adverse events from the manufacturer's submission; and set the HAQ increase defining a response at 0.5 rather than 0.3.
- Optimistic analysis: The ERG used its favourable analysis but also assumed that clinicians escalate the dosages of infliximab, but not abatacept.
- Pessimistic analysis: The ERG used its objective analysis but did not assume that vial sharing for infliximab occurred, and used a linear approach to mapping HAQ to utility as used by Bansback et al (2005).
- Hybrid analysis: The ERG weighted the results of its optimistic and pessimistic scenarios in the ratio of 37:63, with vial sharing in 63% of cases (taken from NICE technology appraisal guidance 195).

3.37 The ERG's analyses showed that the ICER for abatacept plus methotrexate compared with conventional DMARDs varied from £29,552 to £36,045 per QALY gained, and compared with infliximab varied from £29,661 to £63,208 per QALY gained for the 'favourable' and 'pessimistic' scenarios respectively. The ERG noted that the 'objective' analysis showed that the ICER for abatacept plus methotrexate compared with conventional DMARDs was £32,255 per QALY gained, and compared with infliximab was £39,748 per QALY gained.

3.38 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](http://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 abatacept plus methotrexate, having considered evidence on the nature of rheumatoid arthritis and the value placed on the benefits of abatacept plus methotrexate 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 current clinical practice for the treatment of rheumatoid arthritis in the UK. The Committee heard from patient experts that rheumatoid arthritis can severely impact quality of life, and cause pain and depression among people with the disease. The Committee heard that rheumatoid arthritis often affects people's ability to work, and places a considerable burden on carers of people with the disease. Clinical specialists and patient experts emphasised the importance of having a choice of treatment for people whose disease has not responded adequately to initial treatment with conventional DMARDs. The clinical specialists stated that the choice of a biological agent with a mechanism other than inhibiting TNF was important for people who cannot be treated with a TNF inhibitor. The Committee heard from clinical specialists that it is difficult to predict whether a person's disease will respond to a specific drug, or to a specific class of drugs.
- 4.3 The Committee heard that managing rheumatoid arthritis has changed in line with NICE guidance, and that clinicians start second line and subsequent treatment sooner after diagnosis than in the past. Therefore, the characteristics of people treated with biological DMARDs in the UK have changed over time. The Committee heard from the clinical specialists that starting treatment

with a biological DMARD sooner may increase a person's potential to benefit from treatment, because of a reduced likelihood of irreversible joint damage. The Committee noted the differing views of the ERG and the clinical specialists; the ERG's view was that the average participant in the trials had disease of shorter duration than the average UK patient and the clinical specialists' view was that the average participant in the trials had disease of longer duration than the average UK patient. The Committee therefore concluded that there was some uncertainty around the generalisability of estimates of effectiveness from the included trials to the UK population.

- 4.4 The Committee discussed the most appropriate method of assessing response to treatment with biological DMARDs. The Committee heard from clinical specialists that HAQ is not routinely used in clinical practice; DAS is more often used clinically to assess response to treatment, and HAQ is more often used in the research setting. The Committee was aware that DAS28 incorporated assessment of tender and swollen joints as well as biochemical measures of disease activity. The Committee heard from the clinical specialists that HAQ score is affected by both reversible and irreversible components of the disease process, and that longstanding disease lessens the potential for the HAQ score to improve because of irreversible joint damage. The Committee heard from the manufacturer that HAQ was used for consistency with previous NICE technology appraisals related to rheumatoid arthritis, which had also used HAQ. The Committee considered that consistency had merits, but making a decision based on clinically meaningful outcomes was more important. The Committee expressed a preference for DAS28 as an outcome measure in

economic models of rheumatoid arthritis, noting also that clinicians decide to stop or change treatment based on DAS.

- 4.5 The Committee discussed the clinical effectiveness of abatacept with regard to appropriate comparators and subpopulations. The Committee was aware that the scope specified that, in people who had taken at least one conventional DMARD, abatacept plus methotrexate should be compared with other biological DMARDs or conventional DMARDs. The Committee was also aware the manufacturer specifically focussed on an analysis of abatacept plus methotrexate compared with infliximab plus methotrexate in people for whom subcutaneous therapy may be unsuitable. Lastly, the Committee was aware of an additional decision problem proposed by the clinical specialists, comparing abatacept plus methotrexate with conventional DMARDs, but only in people for whom TNF inhibitor treatment is contraindicated.
- 4.6 The Committee noted that the mixed treatment comparison showed that abatacept plus methotrexate had similar efficacy to most of the other biological DMARDs. The Committee also noted that the results of the mixed treatment comparison showed slightly better results for abatacept plus methotrexate than the results observed in the trials included in the meta-analysis (see sections 3.11 and 3.12). In addition, the Committee noted that the manufacturer omitted key trials from the network and included trials with different patient populations. The Committee also considered a consultation comment expressing the concern that one of the trials included people whose disease had inadequately responded to conventional DMARDs other than methotrexate. Therefore the Committee viewed the results of the mixed treatment comparison with caution. The Committee agreed that there was no convincing evidence that

abatacept plus methotrexate was more or less effective than other biological DMARDs plus methotrexate.

- 4.7 The Committee discussed the manufacturer's economic model and was concerned about the use of HAQ score rather than DAS 28, the estimation of utility values, the modelling of disease progression and of adverse events, and the inclusion of productivity costs. The Committee considered how the model incorporated estimates of the effectiveness of the drugs derived from the HAQ score in the mixed treatment comparison. The Committee noted that constructing a mixed treatment comparison and modelling data from the HAQ score was likely to have disproportionately favoured abatacept compared with conventional DMARDs. This was because the results obtained for abatacept plus methotrexate were better than for conventional DMARDs plus methotrexate when using the HAQ score compared with the DAS28 score. However, the Committee agreed that the impact of this, although increasing the uncertainty in the estimates of the ICER, would be small.
- 4.8 The Committee considered the utility estimates provided by the manufacturer and noted that the economic model had not included health-related quality of life measured using a generic preference-based measure, but had instead mapped a disease-specific measure (HAQ) to a generic measure (EQ-5D). The Committee noted that the manufacturer had chosen to do this because mapping HAQ to utilities had been used in the absence of directly elicited EQ-5D data in previous NICE technology appraisals of treatments for rheumatoid arthritis. The Committee noted that the manufacturer's mapping of HAQ scores to EQ-5D utility values resulted in the possibility of clinical scenarios where having rheumatoid arthritis would be worse than being dead. The

Committee heard from the patient experts and noted from the consultation comments that it was possible that some people with rheumatoid arthritis may experience such a low quality of life. The Committee noted that estimates using a non-linear approach to mapping favoured abatacept more than did estimates using a linear approach. It was aware of the manufacturer's sensitivity analysis that showed mapping using a linear utility increased the ICER for abatacept plus methotrexate compared with conventional DMARDs plus methotrexate from £29,700 per QALY gained in the base case to £32,100 per QALY gained. The Committee concluded that although it was not unreasonable to use a non-linear function, the use of a linear function could also be considered plausible, and therefore this increased the uncertainty around the ICERs.

- 4.9 The Committee discussed the manufacturer's assumptions of how rheumatoid arthritis progresses (represented by HAQ score). The model assumed that while a person continues to take a biological DMARD, after an initial improvement, the disease does not get better or worse. The Committee heard from the clinical specialists that this assumption was clinically plausible. However, the Committee heard from the clinical specialists that some people's disease continues to improve, and heard from the patient experts that some people's disease worsens despite ongoing treatment with biological DMARDs. The Committee also noted from the consultation comments that abatacept is unique among biological DMARDs in showing improvement beyond one year. However the Committee was aware that it had not been presented with any data to support this point. The model also assumed that if a person stopped taking a biological DMARD (either because the disease did not respond or because of a serious adverse event), then the HAQ score worsened (rebounded) to the pre-treatment level, after which

the disease progressed at a rate equal to that of a person on a sequence of conventional DMARDs followed by palliative care. The Committee heard that the clinical specialists believed that this rebound assumption is likely to underestimate the underlying disease progression. The Committee concluded that incorporating an alternative rebound effect after a person withdraws from treatment with a biological DMARD to a HAQ score worse than pre-treatment level, would be likely to increase the ICER for abatacept plus methotrexate compared with conventional DMARDs. The Committee agreed that the uncertainty about the rebound assumptions added uncertainty to the ICERs.

- 4.10 The Committee noted that the manufacturer excluded costs and disutilities associated with adverse events from the model. The Committee considered that if adverse events occur at different rates for different drugs, then these rates should have been included in the model. The Committee discussed consultation comments stating that adverse event rates with abatacept are lower than for other biological DMARDs. The Committee noted that these comments referred to a recently published network meta-analysis and Cochrane overview, which reported that abatacept was amongst the biological DMARDs for which no increased rate of side effects compared with placebo had been proven in the short term, whereas for others an increased rate was shown. However, the authors of the report expressed caution with interpreting these results because there was no consistency across the outcomes, and concluded that people who take biological DMARDs will probably experience more side effects or drop out of the study due to side effects than people who take placebo. The Committee understood that the trial data presented to Committee showed that overall adverse event rates were similar for abatacept plus

methotrexate and placebo plus methotrexate. However, the Committee was also aware that it had not been presented with comparative long-term adverse event data. The Committee considered that adverse events would be expected to occur with abatacept plus methotrexate more frequently over time than with placebo plus methotrexate. The Committee concluded that in the absence of any long-term comparative adverse event data being presented, there was uncertainty about differences over time in adverse events with abatacept plus methotrexate compared with placebo plus methotrexate.

- 4.11 The Committee considered the costs included in the economic model. The Committee heard the manufacturer acknowledge that it had used costs that included loss of productivity, and that this was outside the reference case defined by NICE. The Committee agreed that the costs proposed by the ERG were more appropriate. The Committee noted that including these costs increased the ERG's corrected base-case ICER from £29,700 to £29,900 per QALY gained.
- 4.12 The Committee was aware that NICE recommends adalimumab plus methotrexate, etanercept plus methotrexate, infliximab plus methotrexate (TA130) or certolizumab pegol plus methotrexate (TA186) as treatment options in the clinical pathway at the same point at which abatacept plus methotrexate was considered in this appraisal. The Committee noted that in all individual comparisons, the subcutaneous therapies dominated abatacept plus methotrexate. It agreed with the manufacturer that, compared with subcutaneously-injected biological DMARDs, abatacept plus methotrexate would not provide a cost-effective use of NHS resources.

4.13 The Committee then considered the decision problem added by the manufacturer, that is, the clinical and cost effectiveness of abatacept plus methotrexate compared with infliximab plus methotrexate in people for whom subcutaneously-injected biological DMARDs are unsuitable. The Committee discussed whether this group represents a clearly defined and identifiable population relevant for clinical practice in the NHS. It heard from the clinical specialists that they were disappointed that the manufacturer focussed on this question, which they felt did not reflect clinical practice. The Committee heard from the clinical specialists that in current practice, route of administration rarely determines which drug to prescribe, although some people do care whether therapies are injected intravenously or subcutaneously. The Committee noted consultation comments that patients may have a strong preference for a certain form of administration. The Committee also heard that the devices used to self-administer subcutaneous injections had improved considerably and that few people experience problems handling the injection devices. The Committee noted that subcutaneous interventions could be administered at home by a nurse or a family member, subject to local decision-making, or in hospitals (as with intravenous infusions), where clinicians could monitor people more closely if required. The Committee was aware that the manufacturer proposed that the population for whom subcutaneous therapy is unsuitable would include people with needle phobia or needle aversion. However, the Committee concluded that people with aversion to needles are likely to have a similar problem with intravenous therapy, and could possibly be assisted by a nurse or family member. The Committee was aware that psychological treatments for needle phobias or aversion exist. On balance, it agreed that there was no clinically plausible reason related to route

of administration that supports limiting the decision problem to this population. Because the Committee considered this decision problem not to be relevant for the NHS it concluded that it would not develop separate recommendations for people for whom self administration of subcutaneously-injected biological DMARDs is unsuitable.

- 4.14 The Committee then considered the decision problem proposed by the clinical specialists, that is, the clinical and cost effectiveness of abatacept in people for whom treatment with a TNF inhibitor is contraindicated, being aware that abatacept has a different mechanism of action to TNF inhibitors. The Committee discussed whether people for whom treatment with a TNF inhibitor is contraindicated represents clearly defined and identifiable population for clinical practice in the NHS and considered the contraindications listed in the SPC for each biological DMARD. The Committee noted that sepsis is a contraindication for all biological DMARDs including abatacept. The Committee was aware that the manufacturer considered that interstitial lung disease is also a contraindication to TNF inhibitors. However, it noted that interstitial lung disease including pulmonary fibrosis is not listed as contraindication in the SPCs for TNF inhibitors. The Committee was aware that moderate to severe congestive heart failure (New York Heart Association class 3 or 4) is a contraindication to treatment with adalimumab, certolizumab pegol, golimumab and infliximab, but congestive heart failure is not listed as a contraindication in the SPC for etanercept. Therefore, the Committee considered that for people with moderate to severe congestive heart failure, etanercept plus methotrexate is the appropriate comparator for abatacept plus methotrexate.

- 4.15 For people with moderate to severe congestive heart failure, the Committee then considered the clinical and cost effectiveness of abatacept plus methotrexate compared with etanercept plus methotrexate. The Committee noted that the manufacturer had not presented any clinical and cost-effectiveness analyses specifically for people with congestive heart failure. Therefore, the Committee explored the treatment effects and ICERs of abatacept plus methotrexate compared with etanercept plus methotrexate as a proxy for the clinical and cost effectiveness in this group. The Committee noted the manufacturer's estimates, as well as the manufacturer's conclusion that etanercept plus methotrexate dominated abatacept plus methotrexate. The Committee concluded that compared with etanercept plus methotrexate, abatacept plus methotrexate would not provide a cost-effective use of NHS resources.
- 4.16 The Committee was aware that although etanercept is not contraindicated in congestive heart failure, the etanercept SPC includes a warning that it should be used with caution in people with congestive heart failure. The Committee noted that tocilizumab is not contraindicated for people with congestive heart failure, but that existing NICE guidance 'Tocilizumab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 198) recommends it only at a later stage of rheumatoid arthritis treatment than currently being appraised for abatacept. The Committee considered that if etanercept was considered unsuitable, then the appropriate comparator for this decision problem would be conventional DMARDs.
- 4.17 The Committee was aware that it had not been presented with any clinical evidence for abatacept plus methotrexate specifically for the

population for which TNF inhibitors are contraindicated or unsuitable. The Committee noted that the manufacturer considered this patient population to be small, and that only limited data would be available. The Committee further noted that there was no information whether such patients were included in the clinical trial. Nonetheless, the Committee considered the results presented by the manufacturer for the overall trial population and from the mixed treatment comparison, which both showed that abatacept plus methotrexate statistically significantly improved ACR, DAS and HAQ scores compared with placebo plus methotrexate. Therefore, the Committee agreed that abatacept plus methotrexate is clinically effective compared with placebo plus methotrexate as assessed in the trial population, However, the Committee was unconvinced that these results are directly transferable to population for whom TNF inhibitors are contraindicated, particularly as people with moderate to severe heart failure have complex medical needs. It concluded that there was no evidence on how much clinical benefit abatacept plus methotrexate may provide in this population.

- 4.18 The Committee noted that no ICERs for abatacept plus methotrexate in people with moderate to severe heart failure had been presented by the manufacturer and therefore explored if the ICERs presented by the manufacturer for abatacept plus methotrexate compared with conventional DMARDs could be used as a proxy for the cost effectiveness of abatacept in this group. The Committee considered the uncertainties in the manufacturers modelling approach (see sections 4.7 to 4.11). In addition, the Committee noted that, because of the prognosis for people with moderate to severe heart failure, a shorter time horizon would have to be adopted. It noted that reducing the time horizon to 5 years increased the manufacturer's base-case ICER from £29,900 to

£84,400 per QALY gained. Furthermore, the Committee was not persuaded that it was appropriate to assume that this group of people would gain the same quality of life benefit from abatacept as the overall patient population and that it would therefore not be appropriate to adopt the overall trial data to this group of people. Therefore, the Committee concluded that an ICER in this situation would likely to be much higher than what is normally considered to be an appropriate use of NHS resources, but that because of the lack of evidence it would not be possible to refer to a precise figure. Furthermore, the Committee viewed its exploration of the possible cost effectiveness of abatacept under these circumstances as only indicative. More importantly, the Committee did not consider it appropriate to provide a separate recommendation for the use of a technology in a group of people for whom no evidence of clinical benefit was available and whose health status is not comparable to the overall trial population but who have very complex medical needs.

- 4.19 The Committee considered whether NICE's duties under the equalities legislation required the Committee to alter or add to its recommendations. The Committee noted that the manufacturer explored potential equality issues in its submission and indicated that people who require or request intravenous infusion may do so because of their age, a disability, or their race, and that denying them intravenous treatment would be unfair. The Committee had earlier concluded that devices used to self-administer subcutaneous injections had improved considerably, few people experience problems handling the injection devices, and subcutaneous injections could be administered at home by a nurse or a family member (see section 4.8). Therefore, the Committee

agreed that the manufacturer's definition of this group did not present an equality issue.

4.20 The Committee noted consultation comments that not providing a treatment option for people for whom a TNF inhibitor is contra-indicated would be unfair. The Committee understood that this group constituted people with moderate to severe heart failure in addition to rheumatoid arthritis (see section 4.14). The Committee considered that this group of patients would be likely to be regarded as having a separate, additional disability alongside their disabilities caused by rheumatoid arthritis. The Committee was aware that its recommendation means that no biological treatment is available for this group once conventional DMARDs have failed. The Committee therefore considered whether a more favourable recommendation could be made for this group of people, that is whether abatacept could be recommended specifically for this group. The Committee noted that if the clinical effectiveness in this group of people was assumed to be the same as in the overall trial population, the ICER was several times higher than what is normally considered to be an appropriate use of NHS resources (see section 4.18). However, the Committee agreed that a more important consideration was that there was no evidence how much clinical benefit abatacept may provide in this population. The Committee noted that these patients have very complex medical needs and that any decision on the use of biological treatments in this group would require a careful balance of the potential benefits and harms for the individual patient. For these reasons the Committee concluded that a general positive recommendation for abatacept for this group of people could not be justified. The Committee considered that this group of people has very complex

medical needs which require careful assessment by clinicians on an individual basis.

**Summary of Appraisal Committee's key conclusions**

TAXXX	Appraisal title: Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs	Section
<b>Key conclusion</b>		
<p>Abatacept in combination with methotrexate is not recommended for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has responded inadequately to one or more conventional non-biological disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate.</p>		1.1
<p>Reasons for recommendation:</p>		
<ul style="list-style-type: none"> <li>Based on the evidence available, abatacept plus methotrexate was dominated by the available subcutaneous therapies (that is, subcutaneous therapies were both more effective and less costly).</li> </ul>		4.12
<ul style="list-style-type: none"> <li>The Committee agreed there was no clinically plausible reason related to route of administration that supports limiting the decision problem to people for whom self-administration of subcutaneously-injected biological agents is unsuitable.</li> </ul>		4.13
<ul style="list-style-type: none"> <li>When TNF inhibitors are contraindicated (congestive heart failure) and etanercept is considered unsuitable because of congestive heart failure, an ICER would likely to be much higher than what is normally considered to be an appropriate use of NHS resources, but because of the lack of evidence it is not possible to refer to a precise figure. More importantly, the Committee did not consider it appropriate to provide a separate recommendation for the use of a technology in a group of people for whom no evidence of clinical benefit was available, whose health status is not comparable to the overall trial population, who have very complex medical needs, and where any decision on the use of biological treatments would require a careful balance of the potential benefits and harms for the individual patient.</li> </ul>		4.18/ 4.20
<b>Current practice</b>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>Clinical specialists and patient experts emphasised the importance of having a choice of treatment for people whose disease has not responded adequately to initial treatment with conventional DMARDs. The clinical specialists stated that the choice of a biological agent with a mechanism other than inhibiting TNF was important for people who cannot be treated with a TNF inhibitor.</p>	4.2
	<p>The Committee heard from clinical specialists that it is difficult to predict whether a person's disease will respond to a specific drug, or to a specific class of drugs.</p>	4.2

The technology		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The clinical specialists stated that the choice of a biological agent with a mechanism other than inhibiting TNF was important for people who cannot be treated with a TNF inhibitor.</p> <p>No specific claim of innovation was made in this appraisal.</p>	<p>4.2</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee was aware that NICE recommends adalimumab plus methotrexate, etanercept plus methotrexate, infliximab plus methotrexate (TA130) or certolizumab pegol plus methotrexate (TA186) as treatment options in the clinical pathway at the same point at which abatacept plus methotrexate was considered in this appraisal.</p> <p>The Committee concluded that the question of the cost effectiveness of abatacept plus methotrexate compared with infliximab plus methotrexate for people for whom self-administration of subcutaneously-injected biological DMARDs is unsuitable is not relevant for the NHS.</p> <p>The Committee noted that sepsis is a contraindication for all biological DMARDs, including abatacept and that interstitial lung disease including pulmonary fibrosis is not listed as contraindication in the SPCs for TNF inhibitors. The Committee was aware that moderate to severe congestive heart failure (New York Heart Association class 3 or 4) is a contraindication to treatment with adalimumab, certolizumab pegol, golimumab and infliximab, but congestive heart failure is not listed as a contraindication in the etanercept SPC.</p>	<p>4.12</p> <p>4.13</p> <p>4.14</p>
<p>Adverse effects</p>	<p>The Committee understood that the trial data presented to Committee showed that overall adverse event rates were similar for abatacept plus methotrexate and placebo plus methotrexate. However, the Committee was also aware that it had not been presented with comparative long-term adverse event data. The Committee considered that adverse events would be expected to occur with abatacept plus</p>	<p>4.10</p>

	<p>methotrexate more frequently over time than with placebo plus methotrexate. The Committee concluded that in the absence of any long-term comparative adverse event data being presented, there was uncertainty about differences over time in adverse events with abatacept plus methotrexate compared with placebo plus methotrexate.</p>	
<p><b>Evidence for clinical effectiveness</b></p>		
<p>Availability, nature and quality of evidence</p>	<p>The clinical evidence presented in the manufacturer's submission was derived mainly from four RCTs that compared treatment with abatacept plus methotrexate with placebo plus methotrexate or infliximab plus methotrexate.</p> <p>A mixed treatment comparison was also conducted to compare abatacept plus methotrexate with five biological DMARDs plus methotrexate (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and with placebo plus methotrexate.</p> <p>The Committee noted that the mixed treatment comparison showed that abatacept plus methotrexate had similar efficacy to most of the other biological DMARDs. The Committee noted that the manufacturer omitted key trials from the network and included different patient populations. The Committee also considered a consultation comment expressing the concern that one of the trials included people whose disease had inadequately responded to conventional DMARDs other than methotrexate. Therefore the Committee viewed the results of the mixed treatment comparison with caution.</p> <p>The Committee had not been presented with any clinical evidence for abatacept plus methotrexate specifically for the population for which TNF inhibitors are contraindicated or unsuitable. The Committee noted that the manufacturer considered this patient population to be small, and that only limited data would be available. The Committee further noted that there was no information whether such patients were included in the clinical trial.</p>	<p>3.2</p> <p>3.12</p> <p>4.6</p> <p>4.17</p>

Relevance to general clinical practice in the NHS	The Committee heard that managing rheumatoid arthritis has changed in line with NICE guidance, and that clinicians start treatment with conventional DMARDs or TNF inhibitors sooner after diagnosis than in the past. The Committee concluded that difference in the duration and severity of rheumatoid arthritis could limit the generalisability of estimates of effectiveness from the included trials to the UK population.	4.3
Uncertainties generated by the evidence	The Committee was made aware that DAS is more often used clinically to assess response to treatment, and HAQ is more often used in the research setting. The Committee expressed a preference for DAS28 as an outcome measure in economic models of rheumatoid arthritis, noting also that clinicians decide to stop or change treatment based on DAS.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee agreed that abatacept plus methotrexate is clinically effective compared with placebo plus methotrexate.  The Committee noted that the mixed treatment comparison showed that abatacept plus methotrexate had similar efficacy to most of the other biological DMARDs.	4.17  4.6
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The manufacturer submitted an economic model based on cost-utility analyses run over a lifetime horizon comparing abatacept with three comparators: all other biological DMARDs, conventional DMARDs and infliximab plus methotrexate. The ERG provided a number of scenario analyses.	3.14-3.21  3.36
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the manufacturer's mapping of HAQ scores to EQ-5D utility values resulted in the possibility of clinical scenarios where having rheumatoid arthritis would be worse than being dead.	4.8

	<p>The Committee concluded that incorporating an alternative rebound effect after a person withdraws from treatment with a biological DMARD to a HAQ score worse than pre-treatment level, would be likely to increase the ICER for abatacept compared with conventional DMARDs.</p> <p>The Committee concluded that in the absence of any long-term comparative adverse event data being presented, there was uncertainty about long-term adverse events with abatacept.</p> <p>The Committee heard the manufacturer acknowledge that it had used costs that included loss of productivity, and that this was outside the reference case defined by NICE.</p>	<p>4.9</p> <p>4.10</p> <p>4.11</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee noted that the quality of life and life expectancy before treatment for people for whom treatment with etanercept is considered unsuitable because of congestive heart failure, would be lower, on average, than the estimate used by the manufacturer. The Committee also noted that the economic model had not included health-related quality of life measured using a generic preference-based measure, but had instead mapped a disease-specific measure (HAQ) to a generic measure (EQ-5D). The Committee noted that the manufacturer had chosen to do this because mapping HAQ to utilities had been used in the absence of directly elicited EQ-5D data in previous NICE technology appraisals of treatments for rheumatoid arthritis. The Committee noted that the manufacturer's mapping of HAQ scores to EQ-5D utility values resulted in the possibility of clinical scenarios where having rheumatoid arthritis would be worse than being dead. The Committee heard from the patient experts and noted from the consultation comments that it was possible that some people with rheumatoid arthritis may experience such a low quality of life. The Committee noted that estimates using a non-linear approach to mapping favoured abatacept more than did estimates using a linear approach. It was aware of the manufacturer's sensitivity analysis that showed mapping using a linear utility increased the ICER for abatacept plus methotrexate compared with</p>	<p>4.8</p>

	<p>conventional DMARDs plus methotrexate from £29,700 per QALY gained in the base case to £32,100 per QALY gained. The Committee concluded that although it was not unreasonable to use a non-linear function, the use of a linear function could also be considered plausible, and therefore this increased the uncertainty around the ICERs.</p> <p>No additional health-related benefits were identified that were not in the model.</p>	
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable	-
What are the key drivers of cost effectiveness?	Assumptions on the dose of infliximab and on vial sharing for infliximab, and the length of the time horizon had the largest impact on the ICER.	3.23 3.37
Most likely cost-effectiveness estimate (given as an ICER)	<p>Abatacept plus methotrexate was dominated by the available subcutaneous therapies (that is, subcutaneous therapies were both more effective and less costly).</p> <p>When TNF inhibitors are contraindicated (congestive heart failure) and etanercept is considered unsuitable because of congestive heart failure, an ICER would likely be much higher than what is normally considered to be an appropriate use of NHS resources, but because of the lack of evidence it is not possible to refer to a precise figure.</p>	4.12 4.18
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	Not applicable to this appraisal.	-
End-of-life considerations	Not applicable to this appraisal.	-
Equalities considerations and social value judgements	The Committee noted that the manufacturer explored potential equality issues in its submission and indicated that people who require or request intravenous infusion may do so because of their age, a disability, or their race, and that denying them intravenous treatment would be unfair. The Committee had earlier concluded that devices	4.19

	<p>used to self-administer subcutaneous injections had improved considerably, few people experience problems handling the injection devices, and subcutaneous injections could be administered at home by a nurse or a family member (see section 4.8). Therefore, the Committee agreed that the manufacturer's definition of this group did not present an equality issue.</p> <p>The Committee noted consultation comments that not providing a treatment option for people for whom a TNF inhibitor is contra-indicated would be unfair. The Committee understood that this group constituted people with moderate to severe heart failure in addition to rheumatoid arthritis (see section 4.14). The Committee considered that this group of patients would be likely to be regarded as having a separate, additional disability alongside their disabilities caused by rheumatoid arthritis. The Committee was aware that its recommendation means that no biological treatment is available for this group once conventional DMARDs have failed. The Committee therefore considered whether a more favourable recommendation could be made for this group of people, that is whether abatacept could be recommended specifically for this group. The Committee noted that if the clinical effectiveness in this group of people was assumed to be the same as in the overall trial population, the ICER was several times higher than what is normally considered to be an appropriate use of NHS resources (see section 4.18). However, the Committee agreed that a more important consideration was that there was no evidence how much clinical benefit abatacept may provide in this population. The Committee noted that these patients have very complex medical needs and that any decision on the use of biological treatments in this group would require a careful balance of the potential benefits and harms for the individual patient. For these reasons the Committee concluded that a general positive recommendation for abatacept for this group of people could not be justified. The Committee considered that this group of people has very complex medical needs which require careful assessment by clinicians on an individual basis.</p>	<p>4.20</p>
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## 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](http://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 Related NICE guidance

### Published

- Tocilizumab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 198 (2010). Available from [www.nice.org.uk/guidance/TA198](http://www.nice.org.uk/guidance/TA198)
- Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. NICE technology appraisal guidance 195 (2010). Available from [www.nice.org.uk/guidance/TA195](http://www.nice.org.uk/guidance/TA195)
- Certolizumab pegol for the treatment of rheumatoid arthritis in adults. NICE technology appraisal guidance 186 (2010). Available from [www.nice.org.uk/guidance/TA186](http://www.nice.org.uk/guidance/TA186)
- Rheumatoid arthritis: the management of rheumatoid arthritis in adults. NICE clinical guideline 79 (2009). Available from [www.nice.org.uk/guidance/CG79](http://www.nice.org.uk/guidance/CG79)
- Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 130 (2007). Available from [www.nice.org.uk/guidance/TA130](http://www.nice.org.uk/guidance/TA130)

### Under development

NICE is developing the following guidance (details available from [www.nice.org.uk](http://www.nice.org.uk)):

- Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. NICE technology appraisal guidance (publication expected June 2011).

## 7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in July 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.

Amanda Adler  
Chair, Appraisal Committee  
June 2011

## **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.

#### **Dr Amanda Adler (Chair)**

Consultant Physician, Addenbrooke's Hospital

#### **Dr Ray Armstrong**

Consultant Rheumatologist, Southampton General Hospital

#### **Dr Jeff Aronson**

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

#### **Dr Peter Barry**

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

**Professor John Cairns**

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

**Dr Mark Chakravarty**

External Relations Director – Pharmaceuticals and Personal Health, Oral Care Europe

**Professor Fergus Gleeson**

Consultant Radiologist, Churchill Hospital, Oxford

**Mrs Eleanor Grey**

Lay member

**Mr Sanjay Gupta**

YPD Service Case Manager, Southwark Health and Social Care, Southwark PCT

**Dr Neil Iosson**

General Practitioner

**Mr Terence Lewis**

Lay Member

**Dr Ruairidh Milne**

Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

**Dr Rubin Minhas**

General Practitioner and Clinical Director, BMJ Evidence Centre

**Dr Peter Norrie**

Principal Lecturer in Nursing, DeMontfort University

**Professor Stephen Palmer**

Professor of Health Economics, Centre for Health Economics, University of York

**Dr Sanjeev Patel**

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**Dr Casey Quinn**

Lecturer in Health Economics, Division of Primary Care, University of Nottingham

**Dr John Rodriguez**

Assistant Director of Public Health, NHS Eastern and Coastal Kent

**Mr Alun Roebuck**

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

**Dr Florian Alexander Ruths**

Consultant Psychiatrist and Cognitive Therapist at the Maudsley Hospital, London

**Mr Navin Sewak**

Primary Care Pharmacist, NHS Hammersmith and Fulham

**Mr Roderick Smith**

Finance Director, West Kent Primary Care Trust

**Mr Cliff Snelling**

Lay Member

**Professor Ken Stein (Vice Chair)**

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

**Professor Andrew Stevens**

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

***B 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.

**Scott Goulden**

Technical Lead

**Rebecca Trowman**

Technical Adviser

**Jeremy Powell**

Project Manager

## Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research, Sheffield:

- Lloyd Jones M, Stevenson M, Stevens J. et al. Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs, February 2011

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:

- Bristol-Myers Squibb

II Professional/specialist and patient/carer groups:

- British Health Professionals in Rheumatology
- British Society for Rheumatology
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health

- Heart of Birmingham Teaching Primary Care Trust
- Telford and Wrekin Primary Care Trust
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Abbott Laboratories
- Astrazeneca UK
- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety - Northern Ireland
- GlaxoSmithKline
- Medicines and Healthcare products Regulatory Agency
- NHS Quality Improvement Scotland
- Pfizer
- sanofi-aventis
- Schering-Plough

C 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 abatacept by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Peter C Taylor, Professor of Experimental Rheumatology and Head of Clinical Trials, nominated by Bristol Myers Squibb Pharmaceuticals – clinical specialist
- Dr Patrick Kiely, Consultant Physician and Rheumatologist, nominated by the British Society for Rheumatology – clinical specialist
- Mrs Ailsa Bosworth, Chief Executive, National Rheumatoid Arthritis Society, nominated by the National Rheumatoid Arthritis Society – patient expert
- Ms Jean Burke, nominated by the National Rheumatoid Arthritis Society – patient expert

D 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.

- Bristol-Myers Squibb