

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying antirheumatic drugs

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

1 Guidance

- 1.1 Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional disease-modifying antirheumatic drugs (DMARDs) only, including methotrexate, if:
- it is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' ([NICE technology appraisal guidance 130](#)), and
 - the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.
- 1.2 Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if:
- it is used as described for other TNF inhibitor treatments in

'Adalimumab, etanercept, infliximab, rituximab and abatacept for

the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' ([NICE technology appraisal guidance 195](#)), and

- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.

1.3 When using DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.

2 The technology

2.1 Golimumab (Simponi, Schering Plough) is a human monoclonal antibody that prevents the binding of TNF to its receptors, thereby neutralising its activity. In October 2009, golimumab, in combination with methotrexate, received a marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drug (DMARD) therapy including methotrexate has been inadequate. The summary of product characteristics (SPC) notes that golimumab has also been shown to improve physical function in this population. In February 2011, the marketing authorisation was amended to indicate that golimumab has also been shown to reduce the rate of progression of joint damage as measured by X-ray when given in combination with methotrexate.

2.2 Golimumab is contraindicated in people with moderate to severe heart failure, hereditary problems of fructose intolerance, active tuberculosis and other severe infections. Before initiating therapy, physicians should evaluate people for prior evidence of hepatitis B

virus infection, and both active and inactive (latent) tuberculosis infection. The SPC reports that the most common adverse reactions are upper respiratory tract infections, including nasopharyngitis, pharyngitis, laryngitis and rhinitis. For full details of adverse effects, contraindications, special warnings and precautions for use, see the SPC.

- 2.3 Golimumab is injected subcutaneously via a pre-filled injection pen. The recommended dosage is 50 mg given once a month, on the same date each month. The SPC states that in people who weigh more than 100 kg whose rheumatoid arthritis does not show an adequate clinical response after three or four doses, the dosage may be increased to 100 mg once a month. The cost of a syringe or pen pre-filled with 50 mg of golimumab is £774.58 ('Monthly Index of Medical Specialities' [MIMS], December 2010). The annual drug cost of golimumab is £9295 (50 mg dose). Costs may vary in different settings because of negotiated procurement discounts.
- 2.4 The manufacturer has agreed a patient access scheme with the Department of Health, in which the 100 mg dose of golimumab will be available to the NHS at the same cost as the 50 mg dose. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Details of the patient access scheme are provided separately from this document as part of the evidence submitted.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of golimumab and reviews of these submissions by the Evidence Review Group (ERG; appendix B).

Clinical effectiveness

- 3.1 The submission considered people who had never received a TNF inhibitor (the DMARD-experienced population) separately from people who had had previous therapy with a TNF inhibitor (the TNF inhibitor-experienced population).

DMARD-experienced population

- 3.2 Two trials with DMARD-experienced participants were included in the submission – a phase III randomised controlled trial (RCT) with four groups (GO-FORWARD) and a phase II dose-ranging trial with five groups (Kay et al. 2008). The trials investigated the efficacy and the dose effect of golimumab. The manufacturer's submission focused on the groups who had received the licensed dosage of 50 mg golimumab monthly.
- 3.3 GO-FORWARD was a multicentre randomised double-blind trial that compared 50 mg golimumab every 4 weeks plus methotrexate (15 mg or more every week) (n = 89) with placebo plus methotrexate (15 mg or more every week) (n = 133). The trial participants had had active rheumatoid arthritis (defined as persistent disease activity with at least four swollen joints and four tender joints) for at least 3 months and had received methotrexate for at least 3 months. The trial included a controlled phase to 24 weeks and an open-label extension to 5 years. Participants whose disease was inadequately controlled in the placebo arm could cross over to the golimumab arm at week 14. All other participants in the placebo arm crossed over to the golimumab arm at week 24. Participants whose disease was inadequately controlled on 50 mg golimumab were able to cross over to the 100 mg golimumab arm.

- 3.4 The primary outcome measures were the proportion of participants with an ACR20 response at 14 weeks and an improvement from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) score at 24 weeks. Secondary outcome measures included ACR20 response at 24 weeks, ACR50 response at 14 and 24 weeks, ACR70 response at 14 and 24 weeks, Disease Activity Score (DAS) 28 at 14 and 24 weeks and improvement from baseline HAQ-DI score at 14 weeks. Health-related quality of life was measured using the SF-36 tool.
- 3.5 A significantly greater proportion of participants who received 50 mg golimumab plus methotrexate had an ACR20 response at 14 weeks compared with participants who received placebo plus methotrexate (55.1% and 33.1% respectively; $p = 0.001$). Improvement in HAQ-DI score at 24 weeks was significantly greater in the 50 mg golimumab plus methotrexate group compared with the placebo plus methotrexate group (median 0.375 and 0.125 respectively; $p < 0.001$).
- 3.6 Following consultation on the appraisal consultation document, the manufacturer provided long-term outcomes data from 52- and 104-week follow-up on ACR responses and on the proportion of participants maintaining a HAQ improvement greater than or equal to 0.25. These data suggested that for the people who continued to receive golimumab the response to treatment was maintained.
- 3.7 The manufacturer also reported that for key secondary endpoints a significantly greater proportion of participants in the 50 mg golimumab plus methotrexate group had a response compared with participants in the placebo plus methotrexate group. An ACR20 response at 24 weeks was seen in 59.6% of the participants who received 50 mg golimumab plus methotrexate compared with 27.8% of the participants who received placebo plus methotrexate

($p < 0.001$). More participants in the 50 mg golimumab plus methotrexate group had an ACR50 response at 24 weeks than in the placebo plus methotrexate group (37.1% and 13.5% respectively; $p < 0.001$). An ACR70 response at 24 weeks was seen in 20.2% of the 50 mg golimumab plus methotrexate group compared with 5.3% of the placebo plus methotrexate group ($p < 0.001$).

- 3.8 The manufacturer submitted SF-36 data from the GO-FORWARD trial following consultation on the appraisal consultation document. At 24 weeks there was a statistically significant improvement in the physical component summary score in people treated with golimumab compared with placebo (mean change 8.23 and 2.54 respectively, $p < 0.001$). There were statistically significant changes in six of the eight domains, including all physical health domains, in people treated with golimumab compared with placebo. Social functioning and role–emotional domains did not show statistically significant improvements in people treated with golimumab compared with placebo. Data on golimumab from 104-week follow-up suggested that changes in SF-36 were maintained.
- 3.9 Following consultation on the appraisal consultation document, 24-week and 52-week radiographic progression data from the GO-FORWARD trial were submitted. This reported no difference in the mean change from baseline in the van der Heijde modified Sharp (vdH-S) score between the 50 mg golimumab group and the placebo group (mean change 0.93 and 1.10 respectively, $p = 0.855$). Median change was reported to be zero in both golimumab and placebo groups. Further 52-week and 104-week follow-up data were provided by the manufacturer. The key data were marked as academic in confidence and so cannot be reported here. The manufacturer noted a number of factors that could

account for the minimal progression rates observed in both the placebo and golimumab groups in the GO-FORWARD trial, including the use of radiographic outcomes as a secondary endpoint, the crossing over of all participants treated with placebo at week 24 and a lower baseline disease activity in the trial compared with trials of other biological therapies.

- 3.10 The manufacturer submitted a subgroup analysis that assessed people with moderate (DAS 28 score of between 3.2 and 5.1) and severe (DAS 28 score greater than 5.1) disease activity from the GO-FORWARD study separately. The analysis reported relative risks for ACR20, ACR50 and ACR70 response at 24 weeks. For people with moderately active rheumatoid arthritis treated with golimumab (n = 18) and placebo (n = 28), the relative risks of achieving an ACR20, ACR50 and ACR70 response with golimumab compared with placebo were 2.67 (95% confidence interval [CI] 1.30 to 5.48), 1.78 (95% CI 0.78 to 4.05) and 3.89 (95% CI 0.84 to 17.95) respectively. For people with severely active rheumatoid arthritis treated with golimumab (n = 71) and placebo (n = 104), the relative risks of achieving an ACR20, ACR50 and ACR70 response with golimumab compared with placebo were 2.00 (95% CI 1.39 to 2.87), 3.33 (95% CI 1.75 to 6.32) and 3.81 (95% CI 1.42 to 10.21) respectively.
- 3.11 The manufacturer reported similar rates of adverse events at 16 weeks in the 50 mg golimumab plus methotrexate and the placebo plus methotrexate groups (68.5% and 60.9% respectively). The incidence of serious adverse events at 16 weeks was 5.6% in the 50 mg golimumab plus methotrexate group and 2.3% in the placebo plus methotrexate group. Long-term safety data were provided by the manufacturer following consultation on the appraisal consultation document. These were 52- and 104-week

safety data in trial participants with psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis who had received treatment with golimumab across all of the original phase III studies. These data were marked as confidential and therefore cannot be reported.

- 3.12 The second trial (Kay et al. 2008) was a multicentre randomised double-blind study, two arms of which compared 50 mg golimumab (every 4 weeks) plus methotrexate (10 mg or more every week) (n = 35) with placebo plus methotrexate (10 mg or more every week) (n = 35). The trial participants had had active rheumatoid arthritis (defined as persistent disease activity with at least six swollen joints and six tender joints) for at least 3 months and had been treated with methotrexate for at least 3 months. The primary outcome was the proportion of people who had an ACR20 response at 16 weeks. Secondary outcomes included ACR20, 50 and 70 responses over time until 52 weeks, numeric index of the ACR response at 16 weeks and DAS28 at 16 weeks.
- 3.13 Primary outcome data were not presented separately for the 50 mg golimumab group in the manufacturer's submission. However, they were available from a published paper, which showed that an ACR20 response at 16 weeks was seen in 60.0% of people who received 50 mg golimumab plus methotrexate and 37.1% of people who received placebo plus methotrexate.
- 3.14 An ACR20 response at 24 weeks was seen in 74.3% of people in the 50 mg golimumab plus methotrexate group and 45.7% of people in the placebo plus methotrexate group. More participants in the 50 mg golimumab plus methotrexate group had an ACR50 response at 24 weeks than participants in the placebo plus methotrexate group (40.0% and 11.4% respectively). An ACR70 response at 24 weeks was seen in 20.0% of participants in the 50 mg golimumab plus methotrexate group and 5.7% of those in

the placebo plus methotrexate group. The ACR20 and 50 responses for the golimumab plus methotrexate group were statistically significantly different from the placebo plus methotrexate group. However, the ACR70 responses were not statistically significantly different between the treatment arms.

- 3.15 In the second trial (Kay et al. 2008) the proportion of participants who experienced at least one adverse event was slightly higher in the 50 mg golimumab plus methotrexate group than in the placebo plus methotrexate group (91.9% and 85.3% respectively).
- 3.16 Following consultation on the appraisal consultation document, the manufacturer provided further data from the trial by Kay et al. (2008) to support the dosage frequency used in the marketing authorisation. The manufacturer provided additional data for the three groups who received golimumab at unlicensed dosages not included in the submission (50 mg and 100 mg once every 2 weeks, and 100 mg once every 4 weeks). The manufacturer reported that no clear dosage–response relationship was observed, and that the lowest dosage regimen (that is, 50 mg once every 4 weeks) had an ACR response similar to that observed in the higher dosages.

TNF inhibitor-experienced population

- 3.17 The manufacturer’s submission included a single phase III randomised double-blind placebo-controlled trial (GO-AFTER) for the TNF inhibitor-experienced population. The trial had three groups and the manufacturer’s submission focused on two of the groups: the placebo group (n = 155) and the group who received 50 mg golimumab (n = 153) rather than the group who received the unlicensed dose of 100 mg golimumab. The trial participants had had active rheumatoid arthritis (defined as persistent disease activity with at least four swollen joints and four tender joints) for at

least 3 months and had been treated with at least one dose of a TNF inhibitor (etanercept, adalimumab or infliximab). People in the trial were not required to take golimumab in combination with another DMARD. Approximately 66% received golimumab in combination with methotrexate.

- 3.18 The primary outcome was the proportion of participants with ACR20 response at 14 weeks. The duration of follow-up was 24 weeks. The secondary outcomes included ACR50, 70 and 90 at 14 weeks, ACR20, 50, 70 and 90 at 24 weeks and change from baseline in HAQ-DI score at 24 weeks. No data were collected for SF-36, and no data were provided for radiographic progression.
- 3.19 A significantly higher proportion of the participants who received 50 mg golimumab had an ACR20 response at 14 weeks compared with placebo (35.3% and 18.1% respectively; $p < 0.001$). An ACR20 response at 24 weeks was seen in 34.0% of participants in the 50 mg golimumab group compared with 16.8% of participants in the placebo group ($p < 0.001$). An ACR50 response at 24 weeks was seen in more participants in the 50 mg golimumab group than in the placebo group (18.3% and 5.2% respectively; $p < 0.001$). An ACR70 response at 24 weeks was seen in 11.8% of participants in the 50 mg golimumab group and 3.2% of those in the placebo group ($p = 0.004$). Change in HAQ-DI from baseline was assessed at 24 weeks. For the 50 mg golimumab group there was a median improvement in HAQ-DI of 0.25. For the placebo group there was no change in the median HAQ-DI score.
- 3.20 No major differences in the number of reported adverse events were evident in the GO-AFTER study at 24 weeks. The number of serious adverse events at 24 weeks was slightly lower in the 50 mg golimumab group than in the placebo group.

3.21 To provide support for the radiographic data from the GO-FORWARD trial, the manufacturer also provided data from the GO-BEFORE trial. The GO-BEFORE trial compared methotrexate plus placebo with golimumab plus methotrexate in participants who had rheumatoid arthritis not previously treated with methotrexate. Intention-to-treat analyses reported a statistically significant difference in mean change from baseline in radiographic progression at week 52 (1.37 in the methotrexate group [n = 160] and 0.74 in the 50 mg golimumab group [n = 159] [p = 0.015]). Analyses of data from the participants who remained on their originally allocated treatment reported a change from baseline in radiographic progression at week 52 of 0.22 in the methotrexate group (n = 9) and 0.06 in the 50 mg golimumab group (n = 99). At week 104 the change from baseline in radiographic progression was 0.40 (n = 10) and -0.10 (n = 99) in each group respectively.

Mixed treatment comparison and indirect comparison

3.22 No head-to-head trials analysing the efficacy of golimumab compared with other active treatment options were available. Therefore the manufacturer searched for trials of comparator interventions and completed mixed treatment and indirect comparison analyses to estimate the relative effect of golimumab versus the comparators. The manufacturer included comparators that had been recommended by NICE at the time of submission. For the DMARD-experienced population comparisons were made with placebo, adalimumab, certolizumab pegol, etanercept and infliximab. For the TNF inhibitor-experienced population comparisons were made with placebo and rituximab. Following consultation on the appraisal consultation document, the manufacturer submitted additional cost-effectiveness analyses for the comparison of golimumab, tocilizumab and abatacept.

However, separate data on the relative clinical effectiveness of

golimumab compared with tocilizumab and abatacept were not provided.

DMARD-experienced population

- 3.23 Twenty trials were included in the mixed treatment comparison for the DMARD-experienced population. The results from the random effects model showed that for each ACR response, golimumab was statistically significantly superior to placebo. In comparison with adalimumab, certolizumab pegol, etanercept or infliximab there were no statistically significant differences in ACR20, ACR50 or ACR70 response rates. However, the point estimates favoured the other TNF inhibitors, except in the comparison with infliximab. For ACR20 the median relative risks and 95% credibility intervals for golimumab were 0.98 (0.55 to 1.46) compared with adalimumab, 0.72 (0.41 to 1.06) compared with certolizumab pegol, 0.93 (0.51 to 1.43) compared with etanercept and 1.05 (0.57 to 1.65) compared with infliximab. For ACR50, the median relative risks and 95% credibility intervals for golimumab were 0.90 (0.40 to 1.76) compared with adalimumab, 0.63 (0.27 to 1.31) compared with certolizumab pegol, 0.98 (0.40 to 1.99) compared with etanercept and 0.99 (0.42 to 2.04) compared with infliximab. For ACR70, the median relative risks and 95% credibility intervals for golimumab were 0.75 (0.28 to 1.86) compared with adalimumab, 0.47 (0.16 to 1.35) compared with certolizumab pegol, 0.32 (0.09 to 1.15) compared with etanercept and 1.16 (0.40 to 3.00) compared with infliximab.
- 3.24 Sensitivity analyses were performed for ACR20 and ACR50 responses in which the TEMPO etanercept trial was excluded because of a greater response within its placebo arm compared with other studies. The exclusion of the TEMPO trial resulted in raised relative risks for ACR20 and ACR50, indicating increased

efficacy for etanercept in comparison with golimumab. However, these results were statistically significant only in the fixed effects model for the ACR20 response. Exclusion of the TEMPO trial also altered the estimates of relative risk for golimumab in comparison with the other treatments. When golimumab was compared with certolizumab pegol, the differences were statistically significant in the fixed effects model and for ACR20 in the random effects model, with both favouring certolizumab pegol.

- 3.25 A mixed treatment comparison was carried out for selected safety outcomes. Golimumab was estimated to be associated with a greater number of serious adverse events than all comparators except certolizumab pegol. However, none of the differences was statistically significant, and all had wide credibility intervals. The estimated rate of serious infections for golimumab was similar to the rates for infliximab and etanercept, and lower than those for adalimumab and certolizumab pegol. These differences reached statistical significance for the comparison of golimumab with certolizumab pegol. However, all had wide credibility intervals. Golimumab was estimated to have fewer discontinuations because of adverse events. However, this reached statistical significance only in the comparison of golimumab with certolizumab pegol.

TNF inhibitor-experienced population

- 3.26 Two trials were used in the indirect comparison analyses of golimumab (GO-AFTER) and rituximab (REFLEX) for the TNF inhibitor-experienced population. In these analyses (based on the methods developed by Bucher et al. [1997]) golimumab and rituximab were indirectly compared, with placebo as the comparator. Although the estimates of ACR response favoured rituximab, there were no statistically significant differences between golimumab and rituximab. For ACR20 the relative risk was 0.71

(95% CI 0.42 to 1.20). For ACR50 and ACR70 the corresponding figures were 0.66 (95% CI 0.25 to 1.76) and 0.30 (95% CI 0.05 to 1.66).

- 3.27 The indirect comparison suggested that the relative risks of serious adverse events were similar for golimumab and rituximab, although these were associated with wide confidence intervals. The relative risk estimate for serious infections was slightly lower for golimumab compared with rituximab but this difference was not statistically significant. Golimumab was associated with statistically significantly lower rates of discontinuation due to adverse events.

Review from the ERG

- 3.28 The ERG considered the clinical effectiveness review methods and results to be reasonably clearly presented, with adequate systematic searches conducted. The ERG stated that all the relevant RCTs for golimumab and the comparators appeared to have been included and the golimumab trials were of reasonable methodological quality. The ERG considered that the mixed treatment comparisons and indirect comparisons used appropriate trials.
- 3.29 The ERG commented that the populations in GO-FORWARD and Kay et al. (2008) were generally representative of the UK population with rheumatoid arthritis, although in the GO-FORWARD trial the proportion of people who received glucocorticoid therapy was higher than the UK average. Similarly, steroid use in the GO-AFTER population may have been higher than the average in the UK population with rheumatoid arthritis, and in this study only 66% of the participants had also received methotrexate.

- 3.30 The ERG noted inconsistencies between the data presented for ACR20 and ACR50 responses in Kay et al. (2008). Different values were presented in the original study publication (week 16) and in the efficacy meta-analyses in the manufacturer's submission. The ERG was unclear how the original efficacy data from Kay et al. (2008) had been derived and handled in the meta-analyses.
- 3.31 The ERG commented on the complexities involved in comparing data across the interventions in the mixed treatment and indirect comparison analyses because response rates can be influenced by changes in patient populations over time. It noted that the certolizumab pegol trials had a higher ratio of ACR responses on active treatment compared with placebo, and these trials may not be comparable with the trials of other TNF inhibitors.
- 3.32 The ERG reviewed the additional data provided by the manufacturer. The ERG welcomed the SF-36 data from the GO-FORWARD trial and confirmed that SF-36 data were not collected in the GO-AFTER trial. The ERG reported that the radiographic progression data from the GO-BEFORE trial appeared to suggest a reduction in progression of structural damage for participants with rheumatoid arthritis not previously treated with methotrexate. The ERG also stated that the summary of the 24-week data from the GO-FORWARD trial was appropriate. The ERG noted that interpretation of the longer-term data from this trial was limited by cross-over between treatments.

Cost effectiveness

- 3.33 The manufacturer provided two sets of cost-effectiveness analyses, the first in the original submission and the second in response to a request from NICE as part of the preliminary recommendations, which was provided after consultation on the appraisal consultation

document. Both sets of analyses were reviewed by the ERG. Following this review and consideration by the Appraisal Committee, the second set of analyses was not considered to form a sufficiently robust basis for decision making because it was not internally consistent. The manufacturer was asked to resubmit these data. The resubmitted data were also reviewed by the ERG. The original submission and the resubmitted data are included in this section.

Original submission

- 3.34 The manufacturer submitted two decision-analytic Markov models, each with a lifetime horizon. Both models evaluated golimumab as part of a sequence of treatments: one evaluated golimumab in a DMARD-experienced population (comparing golimumab with TNF inhibitors and methotrexate in people whose disease had had an inadequate response to two DMARDs) and the other evaluated golimumab in a TNF inhibitor-experienced population (comparing golimumab with rituximab and methotrexate in people whose disease had had an inadequate response to two DMARDs and a TNF inhibitor). All treatments were given in combination with methotrexate. Methotrexate monotherapy was included as a comparator in each model because it represented the placebo arm in the indirect and mixed treatment comparisons. The manufacturer did not include technologies being appraised by NICE at the time of its submission (tocilizumab, abatacept and the use of etanercept, infliximab and adalimumab after the failure of a first TNF inhibitor) as comparators.
- 3.35 On starting treatment, people could have either an ACR20 response, ACR50 response or no response. The probability of response for golimumab and methotrexate monotherapy was derived from the GO-FORWARD and GO-AFTER trials. To derive

efficacies for the other comparators the response for golimumab was adjusted using the relative effects estimated from the mixed treatment and indirect comparison analyses. For each ACR response criterion the corresponding change in HAQ-DI was calculated based on data from the GO-FORWARD and GO-AFTER trials. The HAQ-DI was in turn mapped to EQ-5D with an equation used in NICE technology appraisal guidance 130 ('Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis'). People progressed to the next treatment if they did not have at least an ACR20 response at 6 months, or if they stopped treatment because of a lack of efficacy or an adverse event. In both models, people progressed to leflunomide, gold, azathioprine, ciclosporin and then palliative treatment.

3.36 At the start of the models people were aged 50 years in the DMARD-experienced population and 54 years in the TNF inhibitor-experienced population. HAQ scores for people entering the model were derived from the baseline characteristics of the GO-FORWARD and GO-AFTER trials: 1.41 and 1.58 respectively. While people were receiving a treatment, it was assumed that their disease severity increased over time. This was modelled with an annual worsening of HAQ score (that is, an HAQ progression rate). The HAQ progression rate was 0.045 for a person being treated with DMARDs, 0.00 for TNF inhibitors, 0.045 for rituximab and 0.09 for palliative treatment.

3.37 Costs relating to treatment, administration, monitoring and hospitalisation were included in the economic models using 2006 reference costs and 2008 unit costs. Following a clarification request, the manufacturer incorporated 2008 reference costs and 2009 unit costs. It was assumed that a course of rituximab was given once every 6 months. The cost of joint replacement was not

included in the model. Costs and quality-adjusted life years (QALYs) were discounted at a rate of 3.5%.

3.38 The results from the economic model were presented incrementally with all treatments compared with each other, and for each treatment individually in comparison with methotrexate. The deterministic results for the DMARD-experienced population showed that the incremental cost-effectiveness ratios (ICERs) were £31,464 (£34,030 additional costs and 1.082 additional QALYs) and £31,444 (£37,702 additional costs and 1.199 additional QALYs) per QALY gained for infliximab and certolizumab pegol respectively in comparison with methotrexate, and £25,346 (£31,878 additional costs and 1.258 additional QALYs) per QALY gained for golimumab in comparison with methotrexate. The ICERs for adalimumab and etanercept in comparison with methotrexate were £25,353 (£31,006 additional costs and 1.223 additional QALYs) and £24,514 (£38,339 additional costs and 1.564 additional QALYs) per QALY gained respectively. The incremental analysis showed that infliximab and certolizumab pegol were both dominated by golimumab because golimumab was more effective and less costly. However, adalimumab and golimumab were both extendedly dominated by etanercept. Etanercept generated the most QALYs of any strategy, at a lower cost per QALY ratio (£24,514 per QALY gained in comparison with methotrexate).

3.39 The results for the deterministic base-case analysis of golimumab in a TNF inhibitor-experienced population show that rituximab was dominated by golimumab because golimumab was less costly and more effective (£31 fewer costs and 0.189 additional QALYs). Golimumab compared with methotrexate had an ICER of £28,286 (£16,502 additional costs and 0.583 additional QALYs) per QALY gained whereas rituximab compared with methotrexate had an

ICER of £41,935 (£16,533 additional costs and 0.394 additional QALYs) per QALY gained.

Comments from the ERG on the manufacturer's original submission

- 3.40 The ERG noted that the model results (total costs and QALYs, time in states, HAQ scores and incremental costs and QALYs) appeared plausible given the parameter inputs. It commented that the model was generally of a high quality. The ERG identified some programming errors in the model that it corrected. However, these errors did not change the conclusion in the manufacturer's submission that, compared with methotrexate, golimumab has an ICER that is comparable to other TNF inhibitors but that golimumab is never the most cost-effective TNF inhibitor treatment.
- 3.41 The ERG considered that it would have been appropriate to include ACR70 response data in the model so that all the available clinical evidence is used to evaluate golimumab. The manufacturer justified the exclusion of these data by stating that there was not a statistically significant difference between golimumab and the comparators and that incorporating this outcome would only add an element of uncertainty to the model inputs. The ERG noted that this reason was not justified because there was also no statistically significant difference in the ACR20 and ACR50 response data for golimumab and the comparators, but these data had been included in the model.
- 3.42 The ERG undertook a number of exploratory analyses to address some of its concerns. The original model used 2006 reference costs and 2008 unit costs. However, after clarification, the manufacturer incorporated 2008 reference costs and 2009 unit costs. The ERG used the updated reference and unit costs and found that they had little impact on the incremental costs for the

different treatments in the DMARD-experienced population, and so the resulting ICERs did not change substantially.

- 3.43 The ERG identified an error in the model for infliximab in the DMARD-experienced population, which resulted in a cost being allocated when a person dies. There was also an error in the modelling of HAQ decrements for certolizumab pegol. Correcting the infliximab costs reduced the total cost of infliximab treatment, and it was no longer dominated by adalimumab. Correcting the HAQ decrements for certolizumab pegol meant that it was the optimal intervention instead of etanercept.
- 3.44 The economic model used the response rates from the GO-FORWARD trial to estimate the probability of ACR response and the probability of stopping treatment because of an adverse event at 6 months in the golimumab and methotrexate groups. However, the model used the mixed treatment comparison to estimate the rates of these events for the comparators; this approach excludes the evidence from Kay et al. (2008). In the exploratory analysis the ERG used the mixed treatment comparison, incorporating the evidence from Kay et al. (2008) to estimate the probability of these outcomes in the placebo group, which is used to populate the methotrexate arm of the economic model. Using the mixed treatment comparison rather than the GO-FORWARD study alone to inform the golimumab versus methotrexate comparison did not substantially alter the results.
- 3.45 The cumulative impact of the changes described in sections 3.42–3.44 reduced all the ICERs for all TNF inhibitors in comparison with methotrexate in the DMARD-experienced group. The ICERs for infliximab and certolizumab pegol in comparison with methotrexate were £24,137 and £20,800 per QALY gained. The ICER for golimumab compared with methotrexate was £24,794 per QALY

gained. The ICERs for adalimumab and etanercept in comparison with methotrexate were £24,800 and £23,990 per QALY gained. The incremental analysis suggested that certolizumab pegol including its patient access scheme is the optimal treatment strategy, dominating etanercept and extendedly dominating golimumab, adalimumab and infliximab.

- 3.46 The ERG stated that for the TNF inhibitor-experienced population there was considerable uncertainty in the HAQ progression rate estimates and the re-administration frequency of rituximab. The ERG commented that the manufacturer assumed a HAQ progression rate equal to the rate for DMARDs rather than for TNF inhibitors, which may underestimate the benefit of rituximab. The ERG also commented that the model assumes that rituximab is re-administered every 6 months but it considered that 9 months would be more reflective of current clinical practice. The ERG amended the model so that rituximab had a zero HAQ progression rate (equal to that of TNF inhibitors) rather than the 0.045 that was assumed in the base-case analysis. The ERG also amended the model so that each person received two infusions in the first 6 months and then one infusion every 9 months. The costs were updated as described for the DMARD-experienced population.
- 3.47 The cumulative impact of the changes described in 3.46 reduced the ICERs for golimumab and rituximab in comparison with methotrexate (£28,115 and £10,088 per QALY gained respectively). The incremental analysis showed that rituximab dominated golimumab.
- 3.48 Following comments received during consultation on the appraisal consultation document about the inclusion of the TEMPO study and the TNF inhibitor monotherapy studies in the base-case analysis, the ERG performed sensitivity analyses to assess the impact on

the ICERs of separately excluding the monotherapy studies and the TEMPO study. In an incremental analysis, when the TEMPO study is excluded etanercept is no longer dominated by certolizumab pegol and it becomes the optimum strategy. When the TNF inhibitor monotherapy studies are excluded, the results do not differ substantially from the base case, with certolizumab pegol remaining the optimum strategy.

Resubmitted additional analyses provided by the manufacturer following consultation on the appraisal consultation document

3.49 In response to a request from NICE, the manufacturer provided additional analyses of the cost effectiveness of golimumab. The analyses included:

- incorporation of ACR70 response data and disease progression on palliative treatment reflected as an increase in HAQ score of 0.06 per year in the economic model
- a sensitivity analysis in which SF-36 data are included in the economic model using mapping to SF-6D
- cost-effectiveness results for the comparison of golimumab, abatacept and tocilizumab for the group of people whose disease has responded inadequately to a TNF inhibitor.

3.50 The manufacturer did not provide any analyses that reported the estimates of cost effectiveness of including the 100 mg dose of golimumab for people weighing over 100 kg whose rheumatoid arthritis does not respond to the 50 mg dose. The manufacturer submitted a patient access scheme that would provide the 100 mg dose at the same cost as the 50 mg dose in this population. This scheme has been approved by the Department of Health.

3.51 In the resubmitted analyses (described in 3.58 and 3.59) the manufacturer corrected the internal inconsistencies previously

present in the analyses. The analyses also incorporated the changes made by the ERG in response to the original submission (that is, updated unit costs and corrections to the HAQ decrements for certolizumab pegol and costs for infliximab). The analyses also included ACR70 response data and a progression rate while on palliative treatment of 0.06 HAQ score units a year.

- 3.52 The results from the economic model for the DMARD-experienced population were presented for each treatment in comparison with methotrexate. Including ACR70 response data in the model produced ICERs that were £21,944 and £25,825 per QALY gained for certolizumab pegol and infliximab respectively in comparison with methotrexate, and £26,996 per QALY gained for golimumab in comparison with methotrexate. The ICERs for adalimumab and etanercept in comparison with methotrexate were £25,523 and £27,157 per QALY gained respectively.
- 3.53 A sensitivity analysis was provided that included the SF-36 data from the GO-FORWARD study converted to SF-6D. The SF-6D scores were calculated only for ACR20 and ACR50 responses. The results showed that the ICERs were £27,413 and £29,484 per QALY gained for certolizumab pegol and infliximab respectively in comparison with methotrexate and £31,046 per QALY gained for golimumab in comparison with methotrexate. The ICERs for etanercept and adalimumab in comparison with methotrexate were £30,936 and £30,893 per QALY gained respectively.
- 3.54 The results from the economic model for the TNF inhibitor-experienced population were presented for golimumab, rituximab abatacept and tocilizumab in comparison with methotrexate. The analyses incorporated a progression rate while on palliative treatment of 0.06 HAQ score units a year, and zero while on

treatment with either golimumab, abatacept or tocilizumab. The progression rate for rituximab was 0.045 HAQ score units per year.

- 3.55 The analyses produced ICERs of £35,288, £32,036 and £35,382 per QALY gained for tocilizumab, golimumab and abatacept respectively in comparison with methotrexate, and £59,328 per QALY gained for rituximab in comparison with methotrexate. One-way sensitivity analyses assuming that people on rituximab experienced no disease progression while on treatment reduced the ICER for rituximab compared with methotrexate to £24,683 per QALY gained. An alternative one-way sensitivity analysis that assumed re-treatment with rituximab every 9 months reduced the ICER for rituximab to £28,047 per QALY gained in comparison with methotrexate.

ERG comments on the manufacturer's resubmitted additional analyses

- 3.56 The ERG stated that the results from the manufacturer's resubmitted analyses were consistent with the electronic models provided. The ERG confirmed that the changes reported to have been implemented by the manufacturer had been completed appropriately and that errors previously identified had been corrected. The ERG noted that the results provided were deterministic and that no incremental analyses were included.
- 3.57 For the DMARD-experienced population, the ERG re-ran the manufacturer's model using a probabilistic analysis and presented the results incrementally. The incremental probabilistic analysis suggested that certolizumab pegol was the most cost-effective option, with an ICER in comparison with methotrexate of £22,693 per QALY gained. All other treatments were either dominated or extendedly dominated by certolizumab pegol. For each of the other treatments in comparison with methotrexate the probabilistic analysis produced ICERs for infliximab, golimumab, adalimumab

and etanercept of £25,541, £27,946, £25,951, and £27,129 per QALY gained respectively.

- 3.58 The ERG reviewed the sensitivity analysis provided by the manufacturer that used the SF-36 values converted to SF-6D. The ERG noted that the manufacturer had not directly used the SF-6D values for the placebo and methotrexate group; rather, it had estimated the ratio between the HAQ scores from the two groups in the clinical trial and then applied this ratio to the SF-6D scores for the golimumab group to obtain a value for the methotrexate group. The HAQ adjustment resulted in lower SF-6D scores associated with ACR20, ACR50 and ACR70 responses for the methotrexate group compared with the golimumab group. The ERG stated that it was unclear why the manufacturer had chosen this method.
- 3.59 The ERG re-ran the manufacturer's model using a probabilistic analysis and presented the results incrementally. The incremental probabilistic analysis suggested that certolizumab pegol was the most cost-effective option with an ICER in comparison with methotrexate of £27,182 per QALY gained. All other treatments were either dominated or extendedly dominated by certolizumab pegol. For each of the other treatments in comparison with methotrexate the probabilistic analysis produced ICERs for infliximab, golimumab, adalimumab and etanercept of £28,990, £31,420, £30,129, and £30,412 per QALY gained respectively.
- 3.60 The ERG checked the revised model for the TNF inhibitor-experienced population and stated that the changes had been implemented appropriately. The ERG cross-checked the cost-effectiveness estimates in the model with the study papers and relevant NICE technology appraisals and reported that the values used in the model corresponded. The ERG stated that a full validation of the model was not possible. However, the model

maintained internal consistency and the clinical effectiveness results matched those in previous submissions.

3.61 The ERG re-ran the manufacturer's model using a probabilistic analysis. The ICER for golimumab compared with methotrexate was £32,979 per QALY gained. The ICERs for rituximab, abatacept and tocilizumab compared with methotrexate were £68,663, £34,155, and £34,644 per QALY gained respectively. The ERG produced a sensitivity analysis that assumed that the rate of underlying disease progression while on treatment with rituximab was zero (that is, the same assumption as the other biological treatments), and that rituximab was administered every 9 months rather than every 6 months. This reduced the ICER for rituximab in comparison with methotrexate from £68,663 to £12,196 per QALY gained.

3.62 Full details of all the evidence are in the manufacturer's submissions and the ERG reports, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of golimumab, having considered evidence on the nature of rheumatoid arthritis and the value placed on the benefits of golimumab 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 discussed the clinical management of rheumatoid arthritis. The clinical specialists explained that ideally DMARD therapy should be started as early as possible after diagnosis to reduce joint damage, and that for the majority of people therapy

with conventional DMARDs is sufficient. However, they explained that for a small proportion of people conventional DMARDs do not adequately control disease, and for this group of people biological DMARDs such as TNF inhibitors are needed. The Committee heard from the patient experts and clinical specialists that it is not possible to predict which TNF inhibitor will produce the best effect for each person. Therefore people prefer to have a choice of treatments and hence another treatment option would be welcome. The clinical specialists explained that they discuss with patients the different options for treatment and the choice of treatment is a joint decision between the clinician and the patient. The Committee understood that the availability of a range of treatments was valued by clinicians and patients.

- 4.3 The Committee heard from the clinical specialists and the patient experts that golimumab is administered once per month and this may be an advantage for people who have difficulty injecting themselves because of the joint damage caused by the disease and for people who have a fear of injections. The patient experts stated that once-monthly administration may be more convenient if they want to travel, as trips could more easily be planned around once-a-month administration. A once-monthly treatment may also be beneficial for people who experience injection-site reactions. However, the Committee heard from the clinical specialists that the length of the half-life of golimumab may be a disadvantage if a person needs to stop treatment quickly, for example if they had an adverse reaction or had unplanned surgery, since it would take time for the treatment effects (on immunity, for example) to wear off. The Committee accepted that the once-monthly administration of golimumab may be beneficial for people with rheumatoid arthritis.

- 4.4 The Committee discussed the dosing frequency of golimumab in response to comments received during consultation. The Committee noted that evidence regarding the choice of dose had been provided by the manufacturer from a phase II study (Kay et al. 2008). The Committee considered that the data comparing four different doses and schedules of golimumab showed that the dosing regimen of once every 4 weeks had similar ACR response rates to the fortnightly dosing regimen, and that no clear dosage–response relationship was observed. The Committee accepted that the data showed that 50 mg golimumab once every 4 weeks is the minimum effective dosage.

Clinical effectiveness

- 4.5 The Committee considered the evidence on the clinical effectiveness of golimumab in combination with methotrexate and noted that the manufacturer’s submission considered golimumab at two positions in the treatment pathway – after treatment with conventional DMARDs only, and after treatment with both conventional DMARDs and a TNF inhibitor. The Committee heard from clinical specialists how golimumab would fit into the current treatment pathway. It heard that golimumab may be used either as a first TNF inhibitor therapy in people whose disease has not responded to conventional DMARD therapy, or as a second TNF inhibitor therapy in people who have had previous therapy with a TNF inhibitor. Following comments received during consultation regarding the marketing authorisation for golimumab, the manufacturer was asked to confirm whether the marketing authorisation for golimumab includes people who have had previous therapy with a TNF inhibitor. The manufacturer stated that golimumab was approved on the basis of the GO-FORWARD and GO-AFTER studies and that its use in people who have had previous therapy with a TNF inhibitor is consistent with the

marketing authorisation and the evidence. The Committee concluded that the two positions in the treatment pathway as included in the manufacturer's submission were appropriate to be considered in this appraisal.

- 4.6 For people who have previously had only conventional DMARDs, the Committee considered the evidence from the two placebo-controlled trials of golimumab in combination with methotrexate (GO-FORWARD and Kay et al. 2008). It noted that golimumab in combination with methotrexate had greater clinical effectiveness than placebo in combination with methotrexate. The Committee then discussed the mixed treatment comparison presented by the manufacturer in the absence of head-to-head trials comparing the efficacy of golimumab with that of the other available TNF inhibitors. The Committee noted that the mixed treatment comparison suggested that there were no statistically significant differences in ACR20, ACR50 and ACR70 response rates between golimumab and the other TNF inhibitors, and that the credibility intervals around the estimates were wide. The Committee heard from clinical specialists that they considered the different TNF inhibitors to have broadly similar efficacy. The Committee discussed the potential heterogeneity between the studies included in the comparison, recognising concerns about the comparability of the certolizumab pegol studies. It further noted comments received in consultation that it was inappropriate to include the TEMPO study and the TNF inhibitor monotherapy studies in the mixed treatment comparison. However, the Committee noted the sensitivity analyses performed by the ERG, which showed that the exclusion of these studies did not significantly alter the estimates of cost effectiveness. The Committee concluded that, based on the ACR response rates, golimumab had been demonstrated to be more effective than placebo and that there was no convincing

evidence that golimumab was either more or less effective than the other TNF inhibitors.

4.7 The Committee considered the evidence on the clinical effectiveness of golimumab compared with placebo for the people who had had previous treatment with both conventional DMARDs and a TNF inhibitor. It noted that there was a single trial (GO-AFTER) comparing golimumab with placebo and this trial showed that golimumab had greater clinical effectiveness than placebo. The Committee discussed the indirect comparison of golimumab and rituximab performed in the absence of head-to-head trials comparing the efficacy of golimumab with that of rituximab. It agreed that rituximab is an appropriate comparator for this population, although it was aware that since the manufacturer's submission NICE has published technology appraisal guidance recommending the use of tocilizumab, abatacept and a second TNF inhibitor in certain people who have had previous treatment with a TNF inhibitor. The Committee concluded that although the point estimates favoured rituximab, the indirect comparison did not demonstrate any statistically significant differences in clinical efficacy between golimumab and rituximab. The Committee noted that the additional analyses provided by the manufacturer included cost-effectiveness results for the comparison of golimumab, tocilizumab and abatacept in people who have had previous treatment with a TNF inhibitor. However, the Committee noted that separate data on the clinical effectiveness of golimumab compared with tocilizumab and abatacept were not provided.

4.8 The Committee discussed the long-term data for ACR response and proportion of people maintaining a HAQ improvement equal to or greater than 0.25 in the DMARD-experienced population in the GO-FORWARD trial. The Committee noted limitations to the data,

specifically that the trial had a placebo-controlled phase only up to 24 weeks, and included participants in the placebo arm who had crossed over to golimumab at week 14 because their disease was inadequately controlled. Despite these limitations the Committee agreed that the data suggested that the efficacy of golimumab was maintained over the long term. The Committee also discussed the long-term SF-36 data submitted by the manufacturer and accepted that golimumab in combination with methotrexate had been shown to have a positive benefit on health-related quality of life compared with placebo. The Committee concluded that these data suggested that efficacy of golimumab was maintained.

- 4.9 The Committee considered clinical-effectiveness evidence for subgroups of people in the GO-FORWARD trial who had either moderately or severely active rheumatoid arthritis as defined by their baseline DAS28 score. It noted that the analysis was in a small number of people, particularly the subgroup with moderately active rheumatoid arthritis. It further noted that the analysis was post hoc although it had been provided in line with the scope for the appraisal. For these reasons the Committee concluded that there was uncertainty surrounding the results. It noted that the majority of clinical evidence is in people with severely active rheumatoid arthritis.
- 4.10 The Committee discussed the 52- and 104-week radiographic progression data (measured by the vdH-S) from the GO-FORWARD study submitted by the manufacturer following consultation on the appraisal consultation document. It noted that these data showed no statistically significant difference from baseline in vdH-S score between golimumab 50 mg and placebo. The Committee heard from the manufacturer that both groups in the trial had shown minimal radiographic progression, which meant

that golimumab could not improve on the results seen in the placebo group. The Committee noted a number of explanations provided for the minimal progression in both groups, including the short placebo-controlled period, the use of radiographic outcomes as secondary endpoints in relation to the size of the study and lower baseline disease activity levels in the golimumab trials compared with trials of other biological treatments. The Committee then discussed the 52-week radiographic progression data from the GO-BEFORE study provided as supporting evidence for the GO-FORWARD data. It noted that these data had been used to support the licence extension for golimumab. The Committee was not persuaded that the data had demonstrated an absence of underlying radiographic progression while on treatment with golimumab, but it concluded that the data demonstrated that the combination of golimumab and methotrexate reduced the rate of radiographic progression.

- 4.11 The Committee discussed the adverse events seen in the golimumab RCTs and the results from the mixed treatment comparison and the indirect comparison of golimumab and the comparators in both populations. It noted that the data from the mixed treatment and indirect comparisons suggested few statistically significant differences in relative risk between the treatments but that these were associated with considerable uncertainty. It heard from the clinical specialists that there are no long-term adverse event data for golimumab but that they expected the adverse event profile of golimumab to be no different from that of other TNF inhibitors. The clinical specialists suggested that since golimumab is administered once a month, there might be fewer adverse events compared with other TNF inhibitors as a result of the reduced frequency of administration. The Committee concluded that there was uncertainty surrounding the adverse event profile of

golimumab because of the limited long-term data, but that golimumab's adverse event profile had not been shown to be different from that of other TNF inhibitors.

Cost effectiveness

- 4.12 The Committee considered the economic model that evaluated golimumab as part of a sequence of treatments in people who had had previous treatment with conventional DMARDs only and who had not had a previous TNF inhibitor. It noted that, on the whole, the model used similar assumptions to other models submitted in previous appraisals of TNF inhibitors in rheumatoid arthritis, but that there were some differences from the other models, for example the exclusion of ACR70 response data, alternative rates of disease progression while on treatment and alternative methods for deriving estimates of utility. The Committee noted that the ACR70 response data and rates of underlying disease progression, similar to those used in other NICE technology appraisals, had subsequently been appropriately included in a revised economic model.
- 4.13 The Committee considered the utility estimates incorporated in the original model, and noted that the utility was derived from the ACR response, which was converted to a change in HAQ score and then mapped to EQ-5D. The Committee recognised that a similar approach to mapping had been used in previous NICE technology appraisals of biological treatments for rheumatoid arthritis. However, the Committee noted that this was different from the NICE reference case, which recommends inclusion of directly collected utility data. The Committee then discussed the sensitivity analysis submitted by the manufacturer following the consultation on the appraisal consultation document, using the SF-36 data from the GO-FORWARD study. It noted comments from the ERG about

the method that the manufacturer used to generate the SF-6D for the methotrexate group and that the ERG was unclear why this approach had been taken. The Committee considered that a more appropriate method for the analysis would have been to use the data from the placebo group directly. However, it concluded that the sensitivity analysis suggested that the methodology to derive the utility in the base-case analysis had not been shown to be unreasonable.

- 4.14 The Committee discussed the 100 mg dose, which is indicated for people who weigh more than 100 kg and whose rheumatoid arthritis has not responded after three or four doses of golimumab. It noted that evidence for the clinical and cost effectiveness of this dose was not included in the original submission. The Committee understood that even though the proportion of people who received this dose might be quite small, if the acquisition cost was included in the model the ICER for golimumab would be expected to be higher than that estimated in the base case presented by the manufacturer. The Committee noted that following consultation on the appraisal consultation document, the manufacturer did not submit any additional data regarding the 100 mg dose, but instead proposed a patient access scheme that would provide the 100 mg dose at the same cost as the 50 mg dose in people for whom the higher dose is suitable. The Committee recognised that the patient access scheme has been accepted by the Department of Health. The Committee considered that analyses should have been presented both with and without the proposed patient access scheme, but concluded that with the patient access scheme, the manufacturer's analysis including only the costs of the 50 mg dose could be used as a basis for decision making.

4.15 The Committee noted that the economic analysis from the manufacturer had assumed that there was no progression of disease while on treatment with a TNF inhibitor, but that there was progression while on treatment with conventional DMARDs and on palliative treatment. The Committee discussed the progression of disease while on treatment with TNF inhibitors for people who have had therapy with conventional DMARDs only. The Committee considered that an assumption of no progression while on treatment with a TNF inhibitor could be an overestimate of the benefits of treatment. However, it heard from clinical specialists that although no progression on treatment may appear optimistic, findings from long-term studies suggest that it is a reasonable assumption for people whose rheumatoid arthritis responds to treatment. The Committee recognised that similar assumptions had been made in other NICE technology appraisals of TNF inhibitor treatments for rheumatoid arthritis. The Committee was aware of the long-term radiographic progression data submitted by the manufacturer following consultation on the appraisal consultation document (see 4.9). It noted that these data showed that golimumab reduced the rate of radiographic progression, albeit in a different population. The Committee concluded that in line with NICE technology appraisals of other TNF inhibitors, it would be appropriate to consider the estimates of cost effectiveness that assumed no disease progression while on treatment with a TNF inhibitor. However, it considered that this assumption was uncertain and may overestimate the benefits of treatment.

4.16 The Committee then discussed the revised version of the economic model and sensitivity analyses submitted by the manufacturer that included ACR70 response data and a rate of disease progression while on palliative treatment of 0.06 HAQ score units per year. The Committee discussed the ERG's review of the revised model,

noting that the ERG considered that the errors in the previous model had been corrected and changes implemented appropriately. The Committee noted that the ICERs for golimumab were at the upper end of the range of £25,000–£28,000 per QALY gained produced by other drugs in the class; however, the frequency of administration may generate additional health-related benefits. The Committee noted that the 100 mg dose of golimumab was not considered in the economic model, but that because of the patient access scheme (as described in 2.4), the cost of the 100 mg dose would be equal to that of the 50 mg dose. The Committee was persuaded that, on balance, with the patient access scheme golimumab could be considered a cost-effective option for the treatment of rheumatoid arthritis if used in the same way as other TNF inhibitors, as recommended in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' ([NICE technology appraisal guidance 130](#)) and 'Certolizumab pegol for the treatment of rheumatoid arthritis' ([NICE technology appraisal guidance 186](#)).

- 4.17 The Committee considered the economic model for the group of people who have had previous treatment with both conventional DMARDs and a TNF inhibitor. It noted that the base-case analysis showed that rituximab was dominated by golimumab because golimumab was less costly and more effective. It was aware that in this analysis it was assumed that rituximab is re-administered every 6 months. The Committee heard that the ERG considered re-administration of rituximab every 9 months to be more reflective of clinical practice. The Committee further heard from clinical specialists that for people responding to rituximab treatment the re-treatment intervals would be greater than 6 months. The Committee heard from the ERG about the costs for the first year of rituximab treatment that are included in the model. For the first

6 months of treatment, 1.5 courses of rituximab are included and 1 course of rituximab is included for the second 6 months. The Committee heard that it is unclear why a greater number of courses are required in the first 6 months than in subsequent 6-month periods. The Committee concluded that the rituximab costs had been overestimated in the original economic model, and that a re-treatment interval of 9 months is more appropriate.

4.18 The Committee discussed the progression of disease while on treatment for people who have had previous treatment with conventional DMARDs and a TNF inhibitor. It noted that the manufacturer had assumed that the TNF inhibitors all stop progression of disease while on treatment, but that for rituximab it was assumed that the disease continues to worsen while on treatment by an increase of 0.045 per year in HAQ score. It noted that this is the same as the rate used for conventional DMARDs. The Committee heard from the ERG and clinical specialists that this underestimates the benefits of rituximab, and that it would have been more appropriate to assume that, for people whose disease responds to treatment, rituximab reduces the progression of disease to the same extent as the TNF inhibitors. The Committee was not persuaded that it is appropriate to assume a differential rate of underlying progression of disease between rituximab and golimumab, and concluded that this assumption overestimates the cost effectiveness of golimumab compared with rituximab.

4.19 The Committee discussed the results of the manufacturer's revised version of the economic model and the ERG's exploratory analyses for the group of people who have had previous treatment with both conventional DMARDs and a TNF inhibitor, which compared golimumab with rituximab. It agreed that the ERG's amendments to increase the time between treatment intervals for rituximab and

remove the assumption of a differential rate of underlying progression of disease were appropriate. The Committee noted that when these assumptions were changed rituximab was associated with lower costs and more QALYs than golimumab. The Committee therefore concluded that golimumab would not be a cost-effective use of NHS resources in people who have had previous treatment with conventional DMARDs and a TNF inhibitor and for whom rituximab is an appropriate treatment option.

- 4.20 The Committee recognised that in August 2010 NICE published technology appraisal guidance recommending the TNF inhibitors adalimumab, etanercept, infliximab and abatacept, as well as tocilizumab, for people with rheumatoid arthritis who are unable to have rituximab therapy because of contraindications or if rituximab is withdrawn because of an adverse event ('Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' [NICE technology appraisal guidance 195] and 'Tocilizumab for the treatment of rheumatoid arthritis' [NICE technology appraisal guidance 198]). The Committee agreed that it was appropriate to consider this group of people and the treatment options now available to them. The Committee discussed the revised analyses submitted by the manufacturer and noted that these did not include the other TNF inhibitors (that is, adalimumab, etanercept and infliximab), but did include abatacept and tocilizumab. It further noted the manufacturer's rationale that the other TNF inhibitors could not be included because there were no data from RCTs for these agents in this position in the treatment pathway. The Committee noted that the ICERs for golimumab in comparison with methotrexate were similar to those for abatacept and tocilizumab. The Committee understood that both abatacept and tocilizumab had been recommended for this patient group in NICE technology

appraisal guidance (NICE technology appraisal guidance 195 and NICE technology appraisal guidance 198), with most plausible ICERs of between £20,000–30,000 per QALY gained, and that the TNF inhibitors: adalimumab, etanercept and infliximab had also been recommended in this way with ICERs in this range. On balance the Committee considered that the evidence before it indicated that golimumab would be no less cost effective than the other TNF inhibitors when used in this population. Therefore the Committee concluded that with the patient access scheme, golimumab is an appropriate use of NHS resources in people with rheumatoid arthritis who are unable to have rituximab therapy because of contraindications or if rituximab is withdrawn because of an adverse event, if used in the same way as other TNF inhibitors, as recommended in 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' ([NICE technology appraisal guidance 195](#)).

TAXXX	Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying antirheumatic drugs	Section
Key conclusions		
<p>Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional disease-modifying antirheumatic drugs (DMARDs) only, including methotrexate, if:</p> <ul style="list-style-type: none"> it is used as described for other tumour necrosis factor (TNF) inhibitor treatments in ‘Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis’ (NICE technology appraisal guidance 130), and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. 		1.1
<p>Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if:</p> <ul style="list-style-type: none"> it is used as described for other TNF inhibitor treatments in ‘Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor’ (NICE technology appraisal guidance 195), and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. 		1.2
The key drivers for these recommendations were:		
<ul style="list-style-type: none"> in people whose rheumatoid arthritis has had an inadequate response to previous treatment with conventional DMARDs only, the evidence suggests that golimumab has efficacy and cost-effectiveness estimates that are similar to those of the other TNF inhibitors that have been recommended by NICE 		4.16
<ul style="list-style-type: none"> in people whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, and for whom rituximab is appropriate, rituximab is associated with lower costs and more QALYs than golimumab 		4.19
<ul style="list-style-type: none"> in people whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, and for whom rituximab is contraindicated or withdrawn because of an adverse event, the evidence indicated that golimumab would be no less cost effective than abatacept or tocilizumab or the other TNF inhibitors when used in this population. 		4.20
Current practice		
Clinical need of patients including the availability of alternative treatments	The clinical specialists explained that ideally DMARD therapy should be started as early as possible after diagnosis to reduce joint damage and for the majority of people therapy with conventional DMARDs is sufficient. However, for a small proportion of people conventional DMARDs do not adequately control disease, and for this group of people biological DMARDs such as TNF inhibitors are needed.	4.2

	It is not possible to predict which TNF inhibitor will produce the best effect for each person. Therefore people prefer a choice of treatments and another treatment option would be welcome.	
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Golimumab is administered once per month and this may be an advantage for people who have difficulty injecting themselves because of the joint damage caused by the disease and for people who have a fear of injections. Once-monthly administration may be more convenient for people who travel and may be beneficial for people who experience injection-site reactions.	4.3
What is the position of the treatment in the pathway of care for the condition?	Both the marketing authorisation and clinician opinion indicate that golimumab may be used either as a first TNF inhibitor therapy in people whose disease has not responded to conventional DMARD therapy, or as second TNF inhibitor therapy in people who have had previous therapy with a TNF inhibitor.	4.5
Adverse effects	There is uncertainty about the adverse event profile of golimumab in the absence of long-term data. However, the clinical specialists expect the adverse event profile of golimumab to be no different from that of other TNF inhibitors.	4.11
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The manufacturer's submission considered golimumab at two positions in the treatment pathway – after treatment with conventional DMARDs and not a TNF inhibitor, and after treatment with both conventional DMARDs and a TNF inhibitor.	4.5
	For people who had previously had only conventional DMARDs, there were two clinical trials but there were no head-to-head trials between golimumab and other available TNF inhibitors. As a result, the manufacturer had conducted a mixed treatment comparison and an indirect comparison.	4.6
	For the people who had had previous treatment with both conventional DMARDs and a TNF inhibitor, there was a single trial comparing golimumab with placebo. In the absence of head-to-head trials the manufacturer carried out an indirect comparison of golimumab and rituximab.	4.7
Relevance to general clinical practice in the NHS	The relevance of the evidence to the UK population in clinical practice was not identified as an issue.	
Uncertainties generated	For both populations, there were no statistically significant differences in ACR20, ACR50 and ACR70	4.6

by the evidence	response rates between golimumab and the active comparators in the mixed treatment and indirect comparisons. However, the credibility intervals around the point estimates were wide.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee considered clinical-effectiveness evidence for subgroups of people in the GO-FORWARD trial who either had moderately or severely active rheumatoid arthritis as defined by their baseline DAS28 score.	4.9
Estimate of the size of the clinical effectiveness including strength of supporting evidence	<p>The Committee concluded that for people who had previously had only conventional DMARDs, based on the ACR response rates, golimumab had been demonstrated to be more clinically effective than placebo and that there was no convincing evidence that golimumab was either more or less effective than the other TNF inhibitors.</p> <p>For people who had previously had both conventional DMARDs and a TNF inhibitor, the Committee considered that golimumab had greater clinical effectiveness than placebo. It noted that the point estimates for the comparison of rituximab and golimumab favour rituximab but that there are no statistically significant differences in clinical efficacy between golimumab and rituximab.</p>	4.6 4.7
Evidence for cost effectiveness		
Availability and nature of evidence	<p>The economic model evaluated golimumab as part of a sequence of treatments. One model evaluated golimumab in people who had had previous treatment with conventional DMARDs only, and the other in people who had had treatment with both conventional DMARDs and a TNF inhibitor.</p> <p>Revised models were provided following a request for further data to be provided by the manufacturer.</p>	4.12 4.16 and 4.17
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The Committee noted that the economic analysis from the manufacturer had assumed that there was no progression of disease while on treatment with a TNF inhibitor, but that there was progression while on treatment with conventional DMARDs and on palliative treatment. The Committee considered that an assumption of no progression while on treatment with a TNF inhibitor could be an overestimate of the benefits of treatment.</p> <p>The Committee noted that the manufacturer had assumed that the TNF inhibitors all stop progression of disease while on treatment, but that for rituximab it was assumed that the disease continues to worsen while on treatment by an increase of 0.045 per year</p>	4.15 4.18

	<p>Committee therefore concluded that golimumab would not be a cost-effective use of NHS resources in people who have had previous treatment with conventional DMARDs and a TNF inhibitor and for whom rituximab is an appropriate treatment option.</p> <p>For the group of people who have had previous treatment with both conventional DMARDs and a TNF inhibitor and for whom rituximab is contraindicated or withdrawn because of an adverse event, the Committee understood that both abatacept and tocilizumab had been recommended for this patient group, with most plausible ICERs of between £20,000–30,000 per QALY gained, and that adalimumab, etanercept and infliximab had also been recommended in this way with ICERs in this range. On balance the Committee considered that the evidence before it indicated that golimumab would be no less cost effective than the other TNF inhibitors when used in this population. Therefore the Committee concluded that golimumab is an appropriate use of NHS resources in people with rheumatoid arthritis who are unable to have rituximab therapy because of contraindications or if rituximab is withdrawn because of an adverse event.</p>	4.20
Additional factors taken into account		
Patient access schemes (Pharmaceutical Price Regulation Scheme [PPRS])	The manufacturer has agreed a patient access scheme with the Department of Health, in which the 100 mg dose of golimumab will be available to the NHS at the same cost as the 50 mg dose. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.	2.4
End-of-life considerations	The supplementary advice was not relevant to this appraisal.	
Equalities considerations, social value judgements	No equalities issues were raised in the appraisal.	

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide

funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

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

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

6 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
- 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

- Certolizumab pegol for the treatment of rheumatoid arthritis in adults. NICE technology appraisal guidance 186 (2010). Available from 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
- Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 130 (2007). Available from www.nice.org.uk/guidance/TA130

7 Date for review of guidance

- 7.1 The guidance on this technology in people who have had previous treatment with conventional DMARDs only will be reviewed with NICE technology appraisal guidance 130 and 186. The guidance on this technology in people who have had previous treatment with both conventional DMARDs and a TNF inhibitor population will be reviewed with the review of NICE technology appraisal guidance 195 in June 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Clark
Chair, Appraisal Committee
May 2011

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A *Appraisal Committee members*

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

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

Professor Darren Ashcroft

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

Dr Matthew Bradley

Value Demonstration Director, AstraZeneca

Dr Brian Buckley

Lay Member

Professor Usha Chakravarthy

Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast

Professor Peter Clark (Chair)

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Ian Davidson

Lecturer in Rehabilitation, The University of Manchester

Professor Simon Dixon

Senior Lecturer in Health Economics, University of Sheffield

Dr Martin Duerden

Medical Director, Conwy Local Health Board

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology

Dr Jon Fear

Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Paula Ghaneh

Senior Lecturer and Honorary Consultant, University of Liverpool

Niru Goenka

Consultant Physician, Countess of Chester NHS Foundation Trust

Susan Griffin

Research Fellow, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Alison Hawdale

Lay Member

Professor John Hutton

Professor of Health Economics, University of York

Professor Peter Jones

Emeritus Professor of Statistics, Keele University

Dr Steven Julious

Senior Lecturer in Medical Statistics, University of Sheffield

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Rachel Lewis

Doctoral Researcher

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor Jonathan Michaels (Vice Chair)

Professor of Vascular Surgery, University of Sheffield

Professor Femi Oyebode

Professor of Psychiatry & Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Murray D. Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie

Lay Member

Dr Cathryn Thomas

GP and Associate Professor, The University of Birmingham

Dr Lok Yap

Consultant in Acute Medicine & Clinical Pharmacology, Whittington Hospitals NHS Trust

B Guideline representatives

The following individual, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, was invited to attend the meeting to observe and to contribute as an adviser to the Committee.

- Dr Chris Deighton, Rheumatoid Arthritis Management Guideline Development Group

C ***NICE project team***

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

Sally Doss

Technical Lead

Zoe Garrett

Technical Adviser

Kate Moore

Project Manager

Appendix B: Sources of evidence considered by the Committee

- A The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (SchHARR), University of Sheffield:
- Jackson R et al. (2010) Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs: a single technology appraisal. September 2010
- 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:
- MSD
- II Professional/specialist and patient/carer groups:
- National Rheumatoid Arthritis Society
 - British Health Professionals in Rheumatology
 - British Society for Rheumatology
 - Primary Care Rheumatology Society
 - Royal College of Nursing
 - Royal College of Pathologists
 - Royal College of Physicians
- III Other consultees:
- Department of Health

- Northumberland Care Trust
- Torbay Care Trust
- Welsh Assembly Government

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

- Commissioning Support Appraisals Service
- NHS Quality Improvement Scotland
- Abbott Laboratories (adalimumab)
- AstraZeneca UK
- Bristol Myers Squibb
- Pfizer
- Roche Products
- Sanofi Aventis
- MSD
- UCB Pharma
- National Institute for Health Research Health Technology Assessment Programme
- School of Health & Related Research Sheffield (ScHARR)
- National Clinical Guideline Centre (NCGC)

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 Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Chris Deighton, Consultant Rheumatologist, nominated by National Clinical Guideline Centre – clinical specialist
- Professor Rob Moots, Professor of Rheumatology, nominated by British Society for Rheumatology
- Jean Burke, nominated by National Rheumatoid Arthritis Society – patient expert
- Adrienne Yarwood, nominated by 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.

□ MSD