NICE National Institute for Health and Care Excellence

Golimumab for the treatment of ankylosing spondylitis

Issued: August 2011

NICE technology appraisal guidance 233

guidance.nice.org.uk/ta233

Contents

1 Guidance

1.1 Golimumab is recommended as an option for the treatment of severe, active ankylosing spondylitis in adults only if:

- it is used as described for adalimumab and etanercept in 'Adalimumab, etanercept and infliximab for ankylosing spondylitis' (NICE technology appraisal guidance 143) **and**
- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose in accordance with the patient access scheme.

1.2 People currently receiving golimumab for the treatment of severe, active ankylosing spondylitis who do not fulfil the criteria for treatment with adalimumab and etanercept described in NICE technology appraisal guidance 143 should have the option to continue golimumab until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Golimumab (Simponi, MSD) is a human monoclonal antibody that neutralises the activity of tumour necrosis factor alpha (TNF-α) by preventing it from binding to its receptors. Golimumab has a marketing authorisation for the treatment of severe, active ankylosing spondylitis in adult patients whose condition has responded inadequately to conventional therapy.

2.2 Golimumab is contraindicated in people with moderate to severe heart failure, and people with active tuberculosis or other severe infections. Before initiating therapy, healthcare professionals should check for evidence of prior hepatitis B virus infection, and both active and inactive (latent) tuberculosis infection. For full details of side effects and contraindications, see the summary of product characteristics (SPC).

2.3 Golimumab is injected subcutaneously via a pre-filled injection pen. The recommended dose is 50 mg given monthly on the same day of each month. The SPC states that the available data suggest that clinical response is usually achieved within 12–14 weeks of treatment (after three to four doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this period. In people who weigh more than 100 kg and whose ankylosing spondylitis does not show an adequate clinical response after three or four doses, the dose of golimumab may be increased to 100 mg once a month.

2.4 The cost of golimumab is £762.97 for a 50 mg pre-filled injection pen (excluding VAT; from manufacturer May 2011) which is equivalent to an annual cost of £9155.64 (based on the 50 mg dose). Costs may vary in different settings because of negotiated procurement discounts.

2.5 The manufacturer of golimumab 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.

3 The manufacturer's submission

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

3.1 The manufacturer presented evidence on the clinical effectiveness of golimumab for the treatment of severe, active ankylosing spondylitis in adults. The manufacturer undertook a systematic literature review and identified one trial that provided evidence for golimumab compared with placebo: the GO-RAISE trial. Seven other randomised controlled trials were identified that provided evidence for adalimumab (n = 2) and etanercept (n = 5) compared with placebo. In the absence of head-to-head trials, the manufacturer conducted a Bayesian mixed-treatment comparison to estimate the relative effectiveness of the TNF-α inhibitors, using the eight trials identified in the systematic literature review.

3.2 The GO-RAISE trial was a multicentre, double-blind randomised controlled trial in which 356 adults with severe, active ankylosing spondylitis were randomised to receive golimumab 50 mg (138 participants), golimumab 100 mg (140 participants) or placebo (78 participants) every 4 weeks for up to 24 weeks. Participants whose disease had not responded to golimumab 50 mg by week 14 could receive golimumab 100 mg ('early escape') from week 16. At week 24, participants in the placebo group received blinded treatment with golimumab 50 mg every 4 weeks (cross over). Participants who were already receiving treatment with golimumab 50 mg or 100 mg (up to week 24) continued their dosing regimen. Participants were treated through to week 100 and had efficacy and safety assessments through to week 104. The primary outcome was the proportion of patients with more than a 20% improvement in symptoms (including spinal pain and physical function) according to the Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS 20) at week 14. Secondary outcomes included the proportion of patients with ASAS 20, ASAS 40 or ASAS 50/60, and the proportion of patients with an improvement in disease activity (according to the Bath ankylosing spondylitis disease activity index [BASDAI]) of more than 20% (BASDAI 20), 50% (BASDAI 50), 70% (BASDAI 70) or 90% (BASDAI 90) at 24 weeks.

3.3 Participants in the GO-RAISE trial met the modified New York criteria for active ankylosing spondylitis for 3 months or longer before the treatment started. Participants had a BASDAI of at least 4 units (0–10 point scale), a score of at least 4 cm on the spinal pain visual analogue scale (VAS; 0–10 cm scale) and an inadequate disease response to current or previous non-steroidal anti-inflammatory drugs (NSAIDs) or disease-modifying anti-rheumatic drugs (DMARDs). The baseline characteristics of the participants in each treatment group of the GO-RAISE trial were broadly similar.

3.4 The GO-RAISE trial showed that at week 14 participants treated with golimumab 50 mg had statistically significant improvements in symptoms compared with participants receiving placebo in several outcome measures, including ASAS 20 (59.4% versus 21.8%, $p < 0.001$), ASAS 40 (44.9% versus 15.4%, $p < 0.001$) and BASDAI 50 responses (45.9% versus 15.4%, $p < 0.001$). This benefit was maintained through to week 24 with ASAS 20 (55.8% versus 23.1% $p < 0.001$), ASAS 40 (43.5% versus 15.4% $p < 0.001$) and BASDAI 50 responses (50.8% versus 14.7% $p < 0.001$) for golimumab compared with placebo.

3.5 Golimumab (50 mg and 100 mg) was well tolerated by participants in the GO-RAISE trial and was considered to have a comparable safety profile to placebo. Fewer serious adverse events were reported in participants treated with golimumab (results for golimumab 50 mg and 100 mg were combined) compared with those receiving placebo (5.4% versus 6.5% through to week 24). Adverse events leading to treatment discontinuation were reported in 2.5% of participants treated with golimumab (results for golimumab 50 mg and 100 mg were combined) compared with 1.3% of participants in the placebo group.

3.6 To estimate the relative effectiveness of the TNF-α inhibitors relevant to the decision problem (that is, adalimumab and etanercept), the manufacturer conducted Bayesian mixed-treatment comparisons using data pooled from the GO-RAISE trial and the seven other trials (see section 3.1) at two different time points: short-term (16 weeks) and long-term (more than 16 weeks) analyses. Results from the mixed-treatment comparisons indicated that golimumab, etanercept and adalimumab were more clinically effective than placebo

according to BASDAI and the Bath ankylosing spondylitis functional index (BASFI), and also according to ASAS criteria. When the TNF-α inhibitors were compared with each other, most comparisons failed to demonstrate statistically significant differences between golimumab and the comparators; exceptions were a greater reduction in disease activity (BASDAI) for golimumab compared with etanercept (mean difference -0.88; 95% CrI -1.58 to -0.14), and a significant improvement in changes in spinal movement (BASMI) for adalimumab compared with golimumab (mean difference 0.52, 95% CrI 0.23 to 0.80) based on data from short-term follow-up.

3.7 The manufacturer used data from the mixed-treatment analysis to assess the safety of the TNF-α inhibitors. Results from this analysis indicated that none of the TNF-α inhibitors was associated with statistically significantly more severe adverse events or treatment discontinuations than placebo. However the manufacturer stated that the findings should be interpreted with caution given the rarity of discontinuations and severe adverse events in the trials. TNF-α inhibitors were more likely to be associated with injection-site reactions than placebo. No statistically significant differences between golimumab and adalimumab were found in terms of treatment discontinuation (odds ratio 5.52, 95% CrI 0.74 to 54.51), but a statistically significant difference between golimumab and etanercept was identified (odds ratio 5.14, 95% CrI 1.03 to 39.21).

3.8 The manufacturer undertook a systematic search and identified three studies of the cost effectiveness of TNF-α inhibitors compared with conventional treatment. No studies comparing golimumab with conventional treatment were identified. The manufacturer submitted a de novo economic model that consisted of a short-term decision tree and a long-term Markov model comparing golimumab with adalimumab, etanercept and conventional treatment (including NSAIDs and DMARDs). The manufacturer incorporated in the model many of the assumptions from NICE technology appraisal guidance 143. In the base-case model, a decision is made to continue or withdraw TNF-α inhibitors according to BASDAI response at week 12. After the initial decision tree, patients then enter the Markov model with a cycle length of 12 weeks and time horizon of 20 years. If patients are already receiving a TNF-α inhibitor, they either stay on therapy ('on TNF-α inhibitor' state) or discontinue therapy

because of lack of efficacy or adverse effects ('not on TNF-α inhibitor' state). It was assumed that discontinuations occurred at a rate of 15% per year in line with NICE technology appraisal guidance 143. To model the lower disease activity just after discontinuation of TNF-α inhibitor therapy, two 12-week tunnel states ('just discontinued' and 'discontinued') were also incorporated into the model. Patients who are in the health state 'on TNF-α inhibitor' are assumed to have at least a 50% improvement in BASDAI (BASDAI 50) during the first 12 weeks of treatment and do not discontinue. Patients whose condition responds to treatment continue on TNF-α inhibitor treatment. Treatment is discontinued in patients whose condition does not respond to treatment and they are switched to conventional therapy. Patients in the conventional treatment arm in the initial decision tree enter the Markov model in the 'not on TNF-α inhibitor' state. They remain in this state, receiving a fixed combination of NSAIDs and DMARDs, without consideration of response or switching, to avoid complicating the model further. Patients can die at any point in the model ('death state'). The model structure does not allow switching between TNF-α inhibitors, in line with recommendations in NICE technology appraisal guidance 143. The costs and disutilities associated with adverse effects of treatment were included in the model and were assumed to be the same for all treatments (TNF-α inhibitors and conventional therapy). Discounting was applied at a rate of 3.5% for both costs and health effects.

3.9 Disease progression was incorporated in the model using BASDAI and BASFI scores. Data from the GO-RAISE trial were used to develop predictive equations of mean change from baseline in BASDAI and BASFI scores over time. These equations were used for all TNF-α inhibitors and the manufacturer assumed that the scores followed the GO-RAISE data for 2 years before they either levelled off or started to deteriorate. Mortality was included in the model and was considered to be a constant across the comparator treatments at a relative risk of 1.47.

3.10 Although data on general health were collected using the SF-36 survey in the GO-RAISE trial, the manufacturer did not use these to estimate SF-6D utilities on the basis that SF-6D is not in line with the NICE reference case. The manufacturer then attempted to produce an algorithm based on the data recorded in the GO-RAISE trial. However, the manufacturer acknowledged that

a number of key variables (age, sex and treatment effect) did not have the anticipated effects on health-related utility. This was inconsistent with published studies, which demonstrated a measurable relationship between these variables and an individual's health-related quality of life. In the end, the manufacturer decided it was more appropriate to use an algorithm from the assessment report for a previous NICE technology appraisal ('Adalimumab, etanercept and infliximab for ankylosing spondylitis' NICE technology appraisal guidance 143). This incorporated age, sex, BASFI and BASDAI into an equation that mapped these variables to utility scores measured with the EQ-5D instrument.

3.11 The resource costs included in the model were drug acquisition costs, costs associated with the short-term (12 weeks) and long-term management of ankylosing spondylitis, and the cost of treating adverse events. Short-term treatment costs for the initial decision tree were estimated from a survey of four physicians. Long-term costs were based on BASFI scores from the GO-RAISE trial using the regression equation from the NICE assessment report for NICE technology appraisal guidance 143.

3.12 Costs and quality-adjusted life years (QALYs) for golimumab were shown to be comparable with those of other TNF-α inhibitors. The base-case incremental cost-effectiveness ratio (ICER) for golimumab versus conventional care was £26,597 per QALY gained (incremental costs £5119; incremental QALYs 0.1925). The ICER for adalimumab versus conventional care was £26,747 per QALY gained (incremental costs £4934; incremental QALYs 0.1845). The ICER for etanercept versus conventional care was £26,600 per QALY gained (incremental costs £5115; incremental QALYs 0.1923). One-way sensitivity analyses suggested that the ICER for golimumab compared with conventional care was most sensitive to the baseline BASFI score, the price of golimumab and the model time horizon.

3.13 The ERG identified a number of errors in the search strategy used by the manufacturer to identify the evidence of clinical effectiveness. After correcting for these errors, the ERG identified more references that they judged may have included relevant information relating to adverse events associated with golimumab and the comparator treatments. The ERG considered that the

mixed-treatment comparisons conducted by the manufacturer were an appropriate approach to synthesise the available evidence. However, they noted that only one randomised controlled trial for golimumab was available and most of the trials in the mixed-treatment comparison included small patient populations that were largely heterogeneous and may not have been sufficiently similar for pooling of results. In addition, the ERG noted that the definition of management without TNF-α inhibitors (conventional therapy) varied across the trials and therefore it was uncertain whether conventional therapy, as represented by the placebo groups in each trial, was similar to actual patient experience in clinical practice in the UK.

3.14 The ERG identified some errors in the manufacturer's model and expressed concern that the manufacturer had not rigorously tested the internal validity of the model. The ERG also considered that the use of discontinuation and adverse-event rates utilised in the modelling for NICE technology appraisal guidance 143 rather than the mixed-treatment comparison results was arbitrary and had not been adequately justified. In addition, the ERG stated that the utilities in the model (from the regression equation from NICE technology appraisal guidance 143) should be interpreted with caution because the regression coefficient for age was positive, which the ERG considered to be counter-intuitive. The ERG considered that if the manufacturer had used SF-36 data from the GO-RAISE trial to calculate utilities, this would have increased the face validity of the model. In addition, because patients in the GO-RAISE trial could switch to golimumab 100 mg at 16 weeks, which was only accounted for by the effects of treatment and not the costs, the ERG considered that this may have led to the base-case ICER being too optimistic.

3.15 The ERG considered that ankylosing spondylitis required lifetime treatment and therefore thought that the use of a 20-year time horizon in the base-case model was not appropriate. The ERG also questioned the appropriateness of using BASDAI 50 as the measure of response in the model when ASAS 20 was the primary outcome in all of the included trials.

3.16 The ERG considered that estimating the costs of care by relying on the views of four physicians did not represent best practice. The ERG agreed that the costs associated with specific adverse events would be the same for all

comparators; however it did not agree with the manufacturer that the rate of adverse events for all comparators would be the same. The ERG noted that the manufacturer justified this assumption by pointing out that there were no statistically significant differences in adverse events between comparator treatments. However, the ERG considered that the results of the mixed-treatment comparison indicated there were non-statistically significant differences in the rates of adverse events between the TNF-α inhibitors and that therefore these data should have been used in the model.

3.17 The ERG undertook an exploratory analysis using the manufacturer's base-case economic model. In this analysis, all data for response, discontinuation and adverse events were taken from the mixed-treatment comparison. In addition, the ERG considered the impact of changing the time horizon from 20 years to a lifetime (60.1 years) and using ASAS 20 instead of BASDAI 50 as the response measure at week 12. The ERG also corrected the errors identified in the model, and modified the BASFI equations for disease progression. After incorporating the response, discontinuation and adverse-event rates from the mixed-treatment comparison for all TNF-α inhibitors, the revised base-case incremental cost-effectiveness analyses indicated that golimumab was slightly less effective and less costly than the other TNF-α inhibitors (golimumab and adalimumab were extendedly dominated by etanercept). These analyses produced an ICER for golimumab of £26,954 per QALY gained (incremental costs £4134; incremental QALYs 0.1534) compared with conventional treatment.

3.18 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/TA233

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 ankylosing spondylitis 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 noted that currently, adalimumab and etanercept are recommended by NICE as treatment options for people with severe, active ankylosing spondylitis whose condition has responded inadequately to conventional therapy (NICE technology appraisal guidance 143). The Committee heard from the clinical specialists and patient experts that another TNF-α inhibitor would increase the therapeutic options available and allow patients greater choice. The clinical specialists indicated that for patients receiving their first TNF-α inhibitor, approximately 20% may have adverse effects or their condition will not respond adequately to treatment. However, they believed that most of these patients are likely to benefit from trying another TNF-α inhibitor because of differences in the mechanism of action between the agents. The Committee noted that switching between TNF-α inhibitors is not currently recommended in NICE technology appraisal guidance 143, except when intolerance to the first agent occurs in the first 3 months of treatment.

4.3 The Committee heard from the clinical specialists and patient experts that ankylosing spondylitis may have a debilitating effect on quality of life because of pain, decreased mobility and sleep disturbance. Ankylosing spondylitis is a multisystem disease which can have non-skeletal manifestations (including iritis and inflammatory bowel disease) that can be severe. Patients may be unable to work because of their condition. The Committee also heard from the clinical specialists and patient experts that golimumab would allow greater flexibility and decreased discomfort because it is administered only once a month compared with the other subcutaneously administered TNF-α inhibitors which are given more frequently.

4.4 The Committee discussed the results of the GO-RAISE trial, which compared subcutaneous injections of golimumab 50 mg and golimumab 100 mg with placebo, administered every 4 weeks for up to 24 weeks. The Committee noted that, in this trial, patients whose condition had not responded to golimumab 50 mg by week 14 could receive golimumab 100 mg from week 16. The Committee therefore agreed that although the trial had adequately demonstrated the efficacy of the licensed dose (50 mg) of golimumab at 14 weeks, there was uncertainty about the magnitude of the therapeutic effect of the 50 mg dose beyond 16 weeks. However the Committee acknowledged that in clinical practice, treatment with TNF-α inhibitors would be discontinued in the event of inadequate clinical response at 12 weeks, in accordance with NICE technology appraisal guidance 143.

4.5 The Committee discussed the duration of the therapeutic effect of golimumab and heard from the manufacturer that the open-label extension period of the GO-RAISE trial had shown that efficacy was maintained over a 104-week period. The clinical specialists confirmed that when golimumab is used for extended periods in other medical conditions, its efficacy is maintained. The Committee therefore agreed that, despite the lack of data on the long-term efficacy of golimumab from the GO-RAISE trial, there was sufficient evidence to conclude that golimumab was a clinically effective treatment for people with severe, active ankylosing spondylitis.

4.6 The Committee discussed the clinical effectiveness of golimumab in relation to the other currently available TNF-α inhibitors. The Committee noted the result of the manufacturer's mixed-treatment comparison that identified small but non-statistically significant differences between golimumab and the TNF-α inhibitors for most outcomes, including severe adverse events. The Committee also noted that the ERG's analyses indicated that golimumab was more efficacious than etanercept and adalimumab in terms of improvement in BASDAI scores, but that there was a greater risk of treatment discontinuation with golimumab compared with these other treatments. However, the Committee noted that the 95% credible intervals around these estimates were wide and therefore subject to a high degree of uncertainty. The Committee acknowledged that the trials included in the mixed-treatment comparison showed differences between discontinuation rates in patients treated with

placebo or TNF-α inhibitors, and that only a small number of discontinuations were observed in patients receiving placebo in the GO-RAISE trial. However the Committee noted that overall there were only a small number of treatment discontinuations in the trials and therefore comparisons between discontinuation rates for each TNF-α inhibitor should be interpreted with caution as there are insufficient data available to show conclusive comparative rates. The Committee also heard from clinical specialists that in clinical practice a similar efficacy and adverse-events profile to other TNF-α inhibitors has been observed when golimumab is used in its other licensed indications. The Committee concluded that golimumab was comparable to the other TNF-α inhibitors in terms of efficacy, adverse-event profile and risk of treatment discontinuation.

4.7 The Committee then discussed the manufacturer's economic model and the critique by the ERG. The Committee noted the ERG's criticism that the model had not been designed to enable evaluation of the cost effectiveness of the sequential use of TNF-α inhibitors. The Committee heard from the manufacturer that there was no evidence on the efficacy of golimumab when used in sequence with the other TNF-α inhibitors. The Committee also heard from the clinical specialists that there was only limited experience with the sequential use of TNF-α inhibitors in clinical practice, although a patient registry was being established by The British Society for Rheumatology to collect long-term data on the treatment of ankylosing spondylitis. The Committee acknowledged that cost-effectiveness estimates for golimumab would be likely to be different if calculated as primary therapy compared with use after another TNF-α inhibitor. The Committee concluded that the manufacturer's approach to structuring its economic model was appropriate and there was insufficient evidence to consider the clinical and cost effectiveness of sequential use of golimumab after another TNF-α inhibitor.

4.8 The Committee discussed the manufacturer's cost-effectiveness estimates and the exploratory analyses by the ERG. The Committee noted the ERG's criticism of the manufacturer's economic model. The Committee agreed that the ICERs presented were all uncertain to a degree because of the lack of available data on which to estimate the long-term efficacy of golimumab and the other TNF-α inhibitors. In addition, the Committee noted that in all the

analyses the difference in costs and effectiveness estimates between the TNF-α inhibitors was very small and that the drugs were essentially similar in terms of their clinical and cost effectiveness. The Committee noted that the patient access scheme proposed by the manufacturer allowed dose escalation to 100 mg but did not incur additional costs. The Committee heard from the manufacturer that the cost of golimumab had recently been reduced by 1.5%, although this had only a marginal impact on the ICERs. The Committee was persuaded that golimumab had been shown to have comparable efficacy and cost to adalimumab and etanercept. Consequently, the Committee concluded that, despite its reservations about some aspects of the cost-effectiveness evaluation, golimumab could be considered a cost-effective use of NHS resources when it is used as described for adalimumab and etanercept in 'Adalimumab, etanercept and infliximab for ankylosing spondylitis' (NICE technology appraisal guidance 143).

Summary of Appraisal Committee's key conclusions

TA233	**Appraisal title: Golimumab for the treatment of ankylosing spondylitis**	**Section**
Key conclusion		
Golimumab is recommended as an option for the treatment of severe, active ankylosing spondylitis in adults only if: • it is used as described for adalimumab and etanercept in 'Adalimumab, etanercept and infliximab for ankylosing spondylitis' (NICE technology appraisal guidance 143) **and** • the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose in accordance with the patient access scheme. The Committee concluded that, despite its reservations about some aspects of the cost-effectiveness evaluation, golimumab could be considered a cost-effective use of NHS resources when it is used as described for adalimumab and etanercept in 'Adalimumab, etanercept and infliximab for ankylosing spondylitis' (NICE technology appraisal guidance 143).		1.1 4.8
Current practice		

Clinical need of patients, including the availability of alternative treatments	Currently, adalimumab and etanercept are recommended by NICE as treatment options for people with severe, active ankylosing spondylitis whose condition has responded inadequately to conventional therapy (NICE technology appraisal guidance 143). The Committee heard from the clinical specialists and patient experts that another TNF-α inhibitor would increase the therapeutic options available and allow patients greater choice. The clinical specialists indicated that for patients receiving their first TNF-α inhibitor, approximately 20% may have adverse effects or their condition will not respond adequately to treatment. However, they believed that most of these patients are likely to benefit from trying another TNF-α inhibitor because of differences in the mechanism of action between the agents. The Committee noted that switching between TNF-α inhibitors is not currently recommended in NICE technology appraisal guidance 143, except when intolerance to the first agent occurs in the first 3 months of treatment. The main aim of treatment is to reduce the impact of the condition on patients. This includes pain, decreased mobility, disturbed sleep, and decreased opportunities to work.	4.2 4.3
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 (Simponi, MSD) is a tumour necrosis factor alpha (TNF-α) inhibitor. The Committee heard from the clinical specialists and patient experts that golimumab would allow greater flexibility and decreased discomfort because it is administered subcutaneously only once a month compared with the other TNF-α inhibitors which are administered more frequently.	4.3

What is the position of the treatment in the pathway of care for the condition?	Golimumab may be offered to patients with severe active ankylosing spondylitis whose condition has responded inadequately to conventional therapy.	4.2
Adverse effects	The Committee concluded that golimumab was comparable to the other TNF-α inhibitors in terms of efficacy, adverse-event profile and risk of treatment discontinuation.	4.6
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee discussed the results of the GO-RAISE trial, which compared subcutaneous injections of golimumab 50 mg and golimumab 100 mg with placebo, administered every 4 weeks for up to 24 weeks. The manufacturer presented a network meta-analysis to compare golimumab with adalimumab and etanercept.	4.4 4.6
Relevance to general clinical practice in the NHS	The Committee concluded that golimumab was comparable to the other TNF-α inhibitors in terms of efficacy, adverse-event profile and risk of treatment discontinuation.	4.6
Uncertainties generated by the evidence	The Committee agreed that although the GO-RAISE trial had adequately demonstrated the efficacy of the licensed dose (50 mg) of golimumab at 14 weeks, there was uncertainty about the magnitude of the therapeutic effect of the 50 mg dose beyond 16 weeks.	4.4

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	N/A	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that there was sufficient evidence to conclude that golimumab was a clinically effective treatment for people with severe, active ankylosing spondylitis. The Committee agreed that although the GO-RAISE trial had adequately demonstrated the efficacy of the licensed dose (50 mg) of golimumab at 14 weeks, there was uncertainty about the magnitude of the therapeutic effect of the 50 mg dose beyond 16 weeks.	4.5 4.4
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer submitted a de novo economic model that consisted of a short-term decision tree and a long-term Markov model comparing golimumab with adalimumab, etanercept and conventional treatment (including NSAIDs and DMARDs).	3.8
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted the ERG's criticism of the manufacturer's economic model. The Committee agreed that the ICERs presented were all uncertain to a degree because of the lack of available data on which to estimate the long-term efficacy of golimumab and the other TNF-α inhibitors. In addition, the Committee noted that in all the analyses the difference in costs and effectiveness estimates between the TNF-α inhibitors was very small and that the drugs were essentially similar in terms of their clinical and cost effectiveness.	4.8

Incorporation of health-related quality-of-life benefits and utility values 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?	Although data on general health were collected using the SF-36 survey in the GO-RAISE trial, the manufacturer did not use these to estimate SF-6D utilities on the basis that SF-6D is not in line with the NICE reference case. The manufacturer then attempted to produce an algorithm based on the data recorded in the GO-RAISE trial. However, the manufacturer felt that this algorithm lacked face validity because a number of key variables (age, sex and treatment effect) did not have the anticipated effects on health-related utility. This was inconsistent with published studies, which demonstrated a measurable relationship between these variables and an individual's health-related quality of life. In the end, the manufacturer decided it was more appropriate to use an algorithm from the assessment report for a previous NICE technology appraisal ('Adalimumab, etanercept and infliximab for ankylosing spondylitis' NICE technology appraisal guidance 143). No potential health-related benefits were identified that were not included in the economic model.	3.10
Are there specific groups of people for whom the technology is particularly cost effective?	N/A	-
What are the key drivers of cost effectiveness?	The Committee noted that in all the analyses the difference in costs and effectiveness estimates between the TNF-α inhibitors was very small and that the drugs were essentially similar in terms of their clinical and cost effectiveness.	4.8

Most likely cost-effectiveness estimate (given as an ICER)	The revised base-case incremental cost-effectiveness analyses indicated that golimumab was slightly less effective and less costly than the other TNF-α inhibitors (golimumab and adalimumab were extendedly dominated by etanercept). These analyses produced an ICER for golimumab of £26,954 per QALY gained (incremental costs £4134; incremental QALYs 0.1534) compared with conventional treatment.	3.17
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer of golimumab 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.	2.5
End-of-life considerations	N/A	-
Equalities considerations and social value judgements	No equality issues were identified during the scoping process or during the course of 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 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has ankylosing spondylitis and the doctor responsible for their care thinks that golimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 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/TA233).

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 Clinicians should seek to enrol patients with ankylosing spondylitis in The British Society for Rheumatology registry (see section 4.7).

7 Related NICE guidance

Published

- Adalimumab, etanercept and infliximab for ankylosing spondylitis.NICE technology appraisal guidance 143 (2008). Available from www.nice.org.uk/guidance/TA143

8 Review of guidance

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

Andrew Dillon

Chief Executive

August 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 Jane Adam (Chair) Department of Diagnostic Radiology, St George's Hospital

Professor Philip Home (Vice Chair) Professor of Diabetes Medicine, Newcastle University

Professor A E Ades Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Fiona Duncan Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Christopher Earl Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Mr John Goulston Head of Provider Development, NHS London, Southside

Professor Jonathan Grigg Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Peter Heywood Consultant Neurologist, Frenchay Hospital

Dr Ian Lewin Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth Reader in Health Economics, HERG, Brunel University

Dr Alec Miners Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Ann Richardson Lay member

Mr Stephen Sharp Senior Statistician, MRC Epidemiology Unit

Mr Mike Spencer Assistant Director Patient Experience, Cardiff and Vale University Health Board

Professor Iain Squire Consultant Physician, University Hospitals of Leicester

Mr David Thomson Lay member

Dr Luke Twelves General Practitioner, Ramsey Health Centre, Cambridgeshire

Dr John Watkins Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Anthony S Wierzbicki Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Dr Olivia Wu Reader in Health Economics, University of Glasgow

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.

Helen Tucker Technical Lead

Fiona Rinaldi Technical Adviser

Bijal Joshi Project Manager

Appendix B: Sources of evidence considered by the Committee

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

- Riemsma R, Joore M, Van Asselt T, et al. Golimumab for the treatment of ankylosing spondylitis: a single technology appraisal (April 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. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on golimumab by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor

- Merck Sharp & Dohme (MSD)

II Professional/specialist and patient/carer groups:

- Action on Pain
- British Health Professional in Rheumatology
- National Ankylosing Spondylitis Society
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- The British Society for Rheumatology

III Other consultees:

- Department of Health
- Welsh Assembly Government

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

- Abbott Laboratories (adalimumab)
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- National Institute for Health Research Health Technology Assessment Programme
- NHS Quality Improvement Scotland
- Pfizer (etanercept)
- West Midlands Health Technology Assessment Collaboration

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 by providing oral evidence to the Committee.

- Dr Helena Marzo-Ortega – Consultant Rheumatologist and Honorary Senior Lecturer, nominated by the National Ankylosing Spondylitis Society – clinical specialist
- Dr Karl Gaffney – Consultant Rheumatologist, nominated by The British Society for Rheumatology – clinical specialist
- Mr Ben Hoare, nominated by the National Ankylosing Spondylitis Society – patient expert
- Ms Jane Skerrett, nominated by the National Ankylosing Spondylitis 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.

- Merck Sharp & Dohme (MSD)

Changes after publication

February 2014: implementation section updated to clarify that golimumab is recommended as an option for treating ankylosing spondylitis. Additional minor maintenance update also carried out.

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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