NICE National Institute for Health and Care Excellence

NICE guidance

TNF-alpha inhibitors for treating active ankylosing spondylitis and non-radiographic axial spondyloarthritis

Technology appraisal guidance
Published: 1 February 2016

www.nice.org.uk/guidance/ta383

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA233 and TA143.

1 Recommendations

1.1 Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating active ankylosing spondylitis in adults if:

- the condition has a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 4 units or more and a spinal visual analogue scale (VAS) of 4 cm or more, and
- non-steroidal anti-inflammatory drugs (NSAIDs) are not suitable have not controlled the conditions well enough.

  Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently having infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop.

1.2 Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating non-radiographic axial spondyloarthritis in adults if:

- the condition has a BASDAI score of 4 units or more and a spinal VAS of 4 cm or more, and
- NSAIDs have not controlled the condition well enough or are not tolerated.

1.3 The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.

1.4 The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:

- a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units and
- a reduction in the spinal pain VAS by 2 cm or more.

1.5 Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response.

1.6 When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.

2 Clinical need and practice

2.1 Ankylosing spondylitis and non-radiographic axial spondyloarthritis are part of a group of clinically heterogeneous inflammatory rheumatologic diseases known as spondyloarthritis. Spondyloarthritis can be categorised as having either predominantly axial (sacroiliac joints or spine) or peripheral involvement. In people with axial spondyloarthritis, the predominant symptom is back pain with inflammation of the sacroiliac joints (sacroiliitis) or the spine, or both. The onset of symptoms typically occurs in the third decade of life. Damage is progressive and irreversible and there is increased risk of spinal fracture later in life. There may also be peripheral joint involvement or extra-articular manifestations such as uveitis, inflammatory bowel disease and psoriasis.

2.2 Disease is classified as ankylosing spondylitis if changes to the sacroiliac joints or the spine, or both, can be seen on X-ray. These include erosions, sclerosis (thickening of the bone), and partial or total ankylosis (fusion of joints). The prevalence of ankylosing spondylitis is thought to range from 0.05% to 0.23% and it is about 3 times more common in men than in women.

2.3 Not everyone with symptoms of axial spondyloarthritis will have changes that can be seen on X-ray. Disease is then classified as axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (non-radiographic axial spondyloarthritis). Sacroiliitis or inflammation of the spine may be visible on MRI. Limited epidemiological data are available for non-radiographic axial spondyloarthritis, but it affects about equal numbers of men and women.

2.4 Conventional therapy for ankylosing spondylitis and non-radiographic axial spondyloarthritis includes non-steroidal anti-inflammatory drugs and physiotherapy. Tumour necrosis factor (TNF) -alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are typically used when the disease has not responded adequately to conventional therapy.

2.5 In clinical trials of ankylosing spondylitis and non-radiographic axial spondyloarthritis, 3 key disease components are assessed: disease activity, physical function and structural damage. Several assessment tools have been developed to measure these:

- Disease activity is most commonly assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). BASDAI is a validated, composite index that records patients' responses to 6 questions relating to 5 major symptoms: fatigue, axial pain, peripheral pain, stiffness and enthesitis. Responses are recorded on 10 cm visual analogue scales (VAS). An instrument commonly used to assess spinal mobility is the Bath Ankylosing Spondylitis Metrology Index (BASMI). This uses clinical measurements such as the amount of movement achieved when the patient rotates their head (cervical rotation) or reaches towards the floor (lumbar side flexion).
- Physical function is often assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI). BASFI is a patient-assessed, validated, composite index made up of 10 questions that address function and the patient's ability to manage their disease. As with BASDAI, responses are recorded on a 10 cm VAS.
- Structural damage and disease progression in ankylosing spondylitis are usually evaluated by radiography, using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

2.6 Studies of the natural history of ankylosing spondylitis and non-radiographic axial spondyloarthritis show that disease activity (measured by BASDAI) is fairly stable over time and does not change. Physical function (assessed by BASFI) does deteriorate ('progress') over time, but the rate of progression is not constant or predictable. Changes in BASFI scores over time may be partially driven by progression of spinal damage as assessed by mSASSS.

2.7 The Assessment of Spondyloarthritis International Society (ASAS) has developed a set of response criteria that are commonly used in ankylosing spondylitis clinical trials. The ASAS criteria relate to improvement across a set of 4 domains:

- patient global assessment (measured on a 10 cm VAS)
- physical function (measured using BASFI)
- inflammation (using the mean of 2 questions from BASDAI relating to severity and duration of morning stiffness)
- spinal pain (measured on a 10 cm VAS).

An ASAS 20 response (a common primary efficacy outcome in clinical trials) is defined as an improvement of more than 20% and an absolute change of 1 or more points on the 0 to 10 cm VAS in at least 3 of the 4 domains. In the fourth domain, there must be no worsening by a similar amount. Other definitions of ASAS response (ASAS 40, 50 and 70, based on improvements of 40%, 50% and 70% respectively) and an improvement of 50% or more in BASDAI score (BASDAI 50) are also used to measure outcomes in clinical studies.

3 The technologies

3.1 Adalimumab (Humira, AbbVie), certolizumab pegol (Cimzia, UCB Pharma), etanercept (Enbrel, Pfizer), golimumab (Simponi, Merck Sharp & Dohme), and infliximab (Remicade, Merck Sharp & Dohme; Inflectra, Hospira; Remsima,Napp) inhibit the pro-inflammatory cytokine, tumour necrosis factor (TNF) -alpha. TNF-alpha inhibitors may modify the inflammatory process of the disease. Adalimumab, certolizumab pegol, golimumab and infliximab are monoclonal antibodies, and etanercept is a recombinant human TNF-receptor fusion protein.

3.2 Adalimumab, etanercept, golimumab and infliximab have marketing authorisations in the UK for the treatment of adults with severe active ankylosing spondylitis that has responded inadequately to conventional therapy. Certolizumab pegol has a marketing authorisation in the UK for the treatment of 'adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to, non-steroidal anti-inflammatory drugs (NSAIDs)'.

3.3 Adalimumab, certolizumab pegol and etanercept are also licensed for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (non-radiographic axial spondyloarthritis) but with objective signs of inflammation by elevated C-reactive protein and/or magnetic resonance imaging, whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Golimumab has a marketing authorisation for non-radiographic axial spondyloarthritis. However, regulatory approval was received at a late stage in the appraisal process so golimumab was not included for this indication. Infliximab does not currently have a marketing authorisation in the UK for non-radiographic axial spondyloarthritis.

Adalimumab

3.4 Adalimumab is administered by subcutaneous injection. The recommended dose regimen for patients with ankylosing spondylitis, and for patients with non-radiographic axial spondyloarthritis, is 40 mg (given as 1 injection) every other week. The summary of product characteristics recommends that continued

adalimumab therapy should be carefully reconsidered in patients whose disease does not respond within 12 weeks after starting treatment.

3.5 The summary of product characteristics lists the following adverse reactions for adalimumab: infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache, musculoskeletal pain, hepatitis B reactivation, various malignancies and serious haematological, neurological and autoimmune reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.6 The price of adalimumab is £352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8 ml vial (excluding VAT; BNF edition 68). The annual cost of treatment with adalimumab is estimated at £9,156, assuming the patient has 40 mg every other week (see section 3.4). Costs may vary in different settings because of negotiated procurement discounts.

Certolizumab pegol

3.7 Certolizumab pegol is administered by subcutaneous injection. The recommended loading dosage for patients with ankylosing spondylitis, and for patients with non-radiographic axial spondyloarthritis, is 400 mg (given as 2 injections of 200 mg each) at weeks 0, 2 and 4. The recommended maintenance dose regimen is 200 mg every other week or 400 mg every 4 weeks. The summary of product characteristics recommends that continued certolizumab pegol therapy should be carefully reconsidered if there is no evidence of therapeutic benefit within 12 weeks of starting treatment.

3.8 The summary of product characteristics lists the following adverse reactions for certolizumab pegol: infections (including sepsis, pneumonia, tuberculosis, invasive fungal and opportunistic infections), blood and lymphatic system malignancies (including lymphoma and leukaemia), lupus-like syndrome, injection site reactions (erythema, itching, haematoma, pain or swelling), and hepatitis B reactivation. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.9 The price of certolizumab pegol is £357.50 for a 200-mg pre-filled syringe (excluding VAT; BNF edition 68). UCB Pharma has agreed a patient access scheme with the Department of Health. UCB Pharma will provide the first 12 weeks of certolizumab pegol free of charge, which is equivalent to 10 vials. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Assuming the recommended dosage is followed (see section 3.7), the annual cost for first year of treatment with certolizumab pegol is estimated at £10,368 (or with the patient access scheme, £6,793). Costs may vary in different settings because of negotiated procurement discounts.

Etanercept

3.10 Etanercept is administered by subcutaneous injection. The recommended dosage for patients with ankylosing spondylitis, and for patients with non-radiographic axial spondyloarthritis, is 25 mg administered twice weekly or 50 mg administered once weekly. The summary of product characteristics recommends that continued etanercept therapy should be carefully reconsidered in patients whose disease does not respond within 12 weeks of starting treatment.

3.11 The summary of product characteristics lists the following adverse reactions for etanercept: infections (including upper respiratory infections, bronchitis, bladder infections and skin infections, as well as serious infections such as sepsis), injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), allergic reactions, development of auto-antibodies, itching, fever, various malignancies and serious haematological, neurological and autoimmune reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.12 The price of etanercept is £89.38 for a 25-mg pre-filled syringe or a 25-mg vial containing powder for reconstitution (with solvent), and £178.75 for a 50-mg pre-filled pen or pre-filled syringe (excluding VAT; BNF edition 68). The annual cost of treatment with etanercept, using either twice weekly or once weekly dosage frequency (see section 3.10), is estimated at £9,296. Costs may vary in different settings because of negotiated procurement discounts.

Golimumab

3.13 Golimumab is administered by subcutaneous injection. The recommended dose regimen for patients with ankylosing spondylitis is 50 mg once a month, on the same date each month. The summary of product characteristics recommends that continued golimumab therapy should be carefully reconsidered if there is no evidence of therapeutic benefit within 12 to 14 weeks of starting treatment (that is, after 3 to 4 doses). For patients with a body weight greater than 100 kg whose disease does not respond adequately after 4 doses (50 mg each), the summary of product characteristics states that increasing the dosage of golimumab to 100 mg once a month may be considered. If there is still no evidence of therapeutic benefit after 3 to 4 additional doses of 100 mg, continued golimumab therapy should be carefully reconsidered.

3.14 The summary of product characteristics lists the following adverse reactions for golimumab: infections (including sepsis, pneumonia, tuberculosis, and invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, hepatitis B reactivation, congestive heart failure, autoimmune processes (lupus-like syndrome) and haematological reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.15 The price of golimumab is £762.97 for a 50-mg pre-filled pen or pre-filled syringe and £1,525.94 for a 100-mg pre-filled pen (excluding VAT; BNF edition 68). Merck Sharp & Dohme has agreed a patient access scheme with the Department of Health. This will make the 100-mg dose of golimumab 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. Assuming the patient has 50 mg every month, the annual cost of treatment with golimumab is estimated at £9,156. Because of the patient access scheme, this cost would remain the same for patients with a body weight greater than 100 kg whose disease does not respond adequately to the 50 mg per month dosage and who subsequently have monthly doses of 100 mg (see section 3.13).

Infliximab

3.16 Infliximab is administered by intravenous infusion. The recommended dosage for

patients with ankylosing spondylitis is a 5 mg/kg infusion at weeks 0, 2 and 6, then every 6 to 8 weeks. The summary of product characteristics states that if there is no response by 6 weeks (that is, after 2 doses), no additional treatment with infliximab should be given.

3.17 The summary of product characteristics lists the following adverse reactions for infliximab: infections (including upper respiratory tract infections, sepsis, opportunistic infections and tuberculosis), hepatitis B reactivation, congestive heart failure, serum sickness (delayed hypersensitivity reactions), haematological reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, hepatosplenic T-cell lymphoma, and serious infusion reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.18 The NHS list price of the infliximab originator (Remicade) is £419.62 for a 100-mg vial containing powder for reconstitution (excluding VAT; BNF edition 68). For a patient with a body weight of 73 kg, the annual cost for first year of treatment with infliximab therapy (including 3 induction doses) is estimated at between £16,785 and £13,428 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks).

3.19 Biosimilar versions of infliximab (Inflectra, Hospira; Remsima, Celltrion/Napp) have a marketing authorisation in the UK for the same indications. The therapeutic indications, dosage and method of administration for Inflectra and Remsima are identical to those for Remicade. The NHS list price of Inflectra and Remsima is £377.66 for a 100 mg vial. For a patient with a body weight of 73 kg, the annual cost for first year of treatment with Inflectra or Remsima therapy is estimated at between £15,106 and £12,085 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks). The contraindications, adverse reactions and administration schedule of the biosimilars are the same as for infliximab (see sections 3.16 and 3.17), but both biosimilars are subject to additional monitoring in line with standard European Medicines Agency recommendations.

3.20 Infliximab is available to the NHS at contract prices negotiated through the Commercial Medicines Unit. These prices are lower than the list prices but are commercial in confidence.

4 Committee discussion

The Appraisal Committee considered evidence from a number of sources.

Clinical effectiveness

4.1 The Assessment Group conducted a systematic review and identified 24 relevant randomised controlled trials (RCTs): 19 recruited people with ankylosing spondylitis, 4 recruited people with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (non-radiographic axial spondyloarthritis), and 1 recruited both populations. All except 2 of the trials were placebo-controlled. Of the 24 RCTs, 17 had open-label extension studies, with 11 studies having a total duration of at least a year.

4.2 Patients whose disease responded inadequately to, or who could not tolerate, non-steroidal anti-inflammatory drugs (NSAIDs) were included in 12 RCTs. However, in 7 of these, between 80% and 100% of patients had NSAIDs during the trial. In the trials that did not require failure of NSAIDs as an inclusion criterion, a similar proportion of patients had NSAIDs during the trial. A baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of greater than or equal to 4 was used as an inclusion criterion in most trials; however, the Assessment Group commented that average BASDAI scores were high, mostly between 5.5 and 6.6 (on a scale from 0 to 10, 10 being most severe). Bath Ankylosing Spondylitis Functional Index (BASFI) scores and the level of C-reactive protein at baseline also varied across the RCTs, and so did the thresholds used to define elevated C-reactive protein in the trials in non-radiographic axial spondyloarthritis. The Assessment Group noted that higher C-reactive protein levels are associated with an increased likelihood of an improvement of 50% or more in BASDAI score (BASDAI 50) response.

4.3 Of the 20 RCTs in ankylosing spondylitis, 4 were for adalimumab, 1 for certolizumab pegol, 7 for etanercept, 3 for golimumab and 5 for infliximab. Most were conducted in Europe or North America; 4 were conducted in China. Among patients in the included RCTs, 65% to 97% were male, the average age ranged from 27 years to 48 years, and the average duration of disease was 6.8 years to

19.0 years.

4.4 Of the 5 RCTs in non-radiographic axial spondyloarthritis, 2 were for adalimumab, 1 for certolizumab pegol and 1 for etanercept. The Assessment Group also included a trial for infliximab, even though infliximab does not have a marketing authorisation in the UK for non-radiographic axial spondyloarthritis. The Assessment Group stated that this was to inform the relative efficacy of tumour necrosis factor (TNF) -alpha inhibitors in this indication because the dose used in the identified trial was the same as that licensed for ankylosing spondylitis. Three RCTs were multicentre conducted worldwide, 1 was conducted in Germany and 1 was UK based. Among patients in the included RCTs, 45% to 75% were male, the average age ranged from 28.2 years to 38.3 years, and the average duration of disease was 2.4 years to 17.2 years. The Assessment Group noted substantial heterogeneity in the baseline characteristics across the trials, such as variations in C-reactive protein levels and the proportion of patients with MRI changes.

4.5 The Assessment Group synthesised the data on clinical effectiveness using a Bayesian meta-analysis. For both indications, it included RCTs reporting results between 10 and 16 weeks after starting treatment. The Assessment Group excluded 2 studies because they were redundant in a class effect model (a study by Giardina et al.) or did not include any of the relevant comparators needed for meta-analysis (PLANETAS). The Assessment Group analysed the TNF-alpha inhibitors both individually and as a group, assuming a class effect. The Assessment Group chose to use a fixed-effect model for both analyses (this assumes that all the studies estimated exactly the same treatment effect and that the variability between individual study results occurred by chance). Peripheral symptoms were not included as outcomes in the meta-analysis (except for enthesitis) because few data were available.

Ankylosing spondylitis

4.6 The results of the meta-analysis showed a consistent beneficial effect across all 5 TNF-alpha inhibitors at 10 to 16 weeks, compared with placebo. The pooled relative risk (RR) of an Assessment of Spondyloarthritis International Society (ASAS) of 20 (a common primary efficacy outcome in clinical trials) response ranged from 1.80 (certolizumab pegol) to 2.45 (infliximab). For an ASAS 40

(based on improvements of 40% response), the RRs ranged from 2.53 (certolizumab pegol) to 3.42 (adalimumab). For BASDAI 50 the RRs of a response were 3.16 with adalimumab, 3.17 with etanercept, 3.57 with golimumab, 3.60 with certolizumab pegol, and 4.86 with infliximab. The additional reduction in BASDAI and BASFI scores achieved with adalimumab, certolizumab pegol, etanercept and infliximab compared with placebo were all statistically significant and clinically important. Additional reductions in BASDAI scores compared with placebo were 1.46 units with certolizumab pegol, 1.55 units with adalimumab, 1.75 units with etanercept and 2.28 units with infliximab. Additional BASFI reductions were 1.1 units with certolizumab pegol, 1.25 units with adalimumab, 1.43 units with etanercept, 1.45 units with golimumab and 2.16 units with infliximab.

4.7 When TNF-alpha inhibitors were considered as a class, with 1 treatment effect, the meta-analysis showed statistically significant improvements compared with placebo at 10 to 16 weeks for all outcomes (table 1). The Assessment Group reported little evidence of statistical heterogeneity for the key outcomes (ASAS outcomes, BASFI, BASDAI and BASDAI 50) but substantial heterogeneity for other outcomes.

Table 1 Estimated class effect of TNF-alpha inhibitors compared with placebo in ankylosing spondylitis: meta-analysis of outcomes at 10 to 16 weeks (main analysis)

–	Outcome	95% CI
ASAS 20 (RR)	2.21	2.01 to 2.43
ASAS 40 (RR)	3.06	2.52 to 3.76
BASDAI 50 (RR)	3.37	2.75 to 4.16
BASDAI (additional change from baseline).Negative changes in BASDAI, BASFI and BASMI represent improvement (that is, a health benefit)	−1.66	−1.88 to −1.43
BASFI (additional change from baseline).Negative changes in BASDAI, BASFI and BASMI represent improvement (that is, a health benefit)	−1.38	−1.59 to −1.18

–	Outcome	95% CI
BASMI (additional change from baseline).Negative changes in BASDAI, BASFI and BASMI represent improvement (that is, a health benefit)	−0.27	−0.36 to −0.18
SF-36 PCS (additional change from baseline). Positive changes in SF-36 represent improvement (that is, a health benefit)	4.40	3.60 to 5.21
SF-36 MCS (additional change from baseline). Positive changes in SF-36 represent improvement (that is, a health benefit)	1.93	0.12 to 3.72
MASES	−0.54	−0.89 to −0.19

Abbreviations: ASAS, Assessment in Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; RR, relative risk; SF-36 MCS, Short Form 36 mental component summary; SF-36 PCS, Short Form 36 physical component summary.

4.8 The meta-analysis showed no statistically significant differences between the 5 TNF-alpha inhibitors for efficacy outcomes at 10 to 16 weeks. The Assessment Group noted that the meta-analysis results for infliximab at 10 to 16 weeks appeared slightly better than results for the other TNF-alpha inhibitors (although the credible intervals are wide). It suggested that this apparent superiority could be because of infliximab producing a more rapid clinical improvement than the other treatments (but having similar effectiveness in the long term). This conclusion was based on results from a trial by Giardina et al. that compared infliximab with etanercept. In the Giardina et al. trial, the BASDAI and BASFI outcomes at week 12 favoured treatment with infliximab, but by week 48 the results for infliximab and etanercept were almost identical.

4.9 Analysis of long-term efficacy results from open-label extension studies showed that, after about 2 years of treatment, ankylosing spondylitis continues to respond well to TNF-alpha inhibitors in around half of people with the disease. Mean changes from baseline for BASDAI, BASFI and Bath Ankylosing Spondylitis Metrology Index (BASMI, if reported) were generally maintained at clinically

meaningful levels during long-term follow-up. However, the Assessment Group stated that the open-label extension studies produced less reliable data than the RCTs. Results may not reflect clinical practice because some people continued treatment even though their disease did not respond to therapy (contrary to the UK marketing authorisations). Also, some people took the higher dose of golimumab (100 mg) even though their body weight was less than 100 kg (the summary of product characteristics recommends that increasing the dose to 100 mg once a month should only be considered in patients with body weight greater than 100 kg). The Assessment Group also suggested that differences in outcomes may have been because of differences in follow-up protocols rather than true treatment effects. The Assessment Group concluded that the long-term benefit of TNF-alpha inhibitors appears similar across treatments.

4.10 The impact of TNF-alpha inhibitors on spinal damage (that is, radiographic progression assessed by the modified Stoke Ankylosing Spondylitis Spinal Score [mSASSS]) is unclear. There are some data that suggest a benefit from TNF-alpha inhibitors after about 4 years of treatment. The Assessment Group suggested that the uncertainty may be because of a lack of long-term follow-up data and the insensitivity of X-rays as a tool for evaluating disease progression in ankylosing spondylitis.

4.11 The Assessment Group used results from 11 patient registry studies (identified in a separate screening of the systematic review results) to assess the efficacy of sequential treatment with TNF-alpha inhibitors in ankylosing spondylitis. Most of the studies provided data on infliximab, etanercept and adalimumab; less evidence was available for certolizumab pegol and golimumab. The proportion of patients who continued to take their first TNF-alpha inhibitor was around 70% to 80% after 1 year, 65% to 75% after 2 years, 70% after 3 years and 55% after 5 years. Only 3 studies provided efficacy results for people who had switched to a second or third TNF-alpha inhibitor; results showed about a 30% proportional reduction (10% absolute reduction) in the number of people with a BASDAI 50 response to sequential TNF-alpha inhibitors (table 2). In addition, improvements in BASDAI and BASFI reported after a second and third TNF-alpha inhibitor were not as good the improvements achieved with the first TNF-alpha inhibitor, as seen in the largest registry (DANBIO; table 2). Despite a reduction in efficacy with sequential treatment, the Assessment Group highlighted that, on average, people having a third TNF-alpha inhibitor continued treatment for as long as people

having their second (table 2).

Table 2 Efficacy of sequential TNF-alpha inhibitors in ankylosing spondylitis, based on results from the DANBIO registry

–	First TNF-alpha inhibitor (n=1,436)	Second TNF-alpha inhibitor (n=432)	Third TNF-alpha inhibitor (n=137)
BASDAI 50 at 3 months	54%	37%	30%
BASDAI: median change after 3 months of treatment	−3.1	−2.0	−1.3
BASFI: median change after 3 months of treatment	−2.2	−1.6	−1.3
Median time to drug discontinuation (95% CI)	3.1 years (2.6 to 3.7)	1.6 years (1.0 to 2.2)	1.8 years (0.9 to 2.7)

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CI, confidence interval; TNF, tumour necrosis factor.

4.12 The Assessment Group concluded that, despite a decrease in response rates, sequential treatment with TNF-alpha inhibitors can be beneficial for people with ankylosing spondylitis.

Non-radiographic axial spondyloarthritis

4.13 Outcomes for 3 of the 4 treatments in the meta-analysis (certolizumab pegol, etanercept and infliximab) were based on results from single trials of each drug. The RRs, compared with placebo, of an ASAS 20 response were similar for adalimumab, certolizumab pegol and etanercept (ASAS 20 was not reported in the trial of infliximab), ranging from 1.46 to 1.92. The RRs of a BASDAI 50 response (compared with placebo) was 1.92 with etanercept, 2.52 with adalimumab and 2.80 with certolizumab pegol. A greater variation in results was seen in the ASAS 40 response and reductions in BASDAI and BASFI. For ASAS 40 the RRs ranged from 2.07 (etanercept) to 3.63 (infliximab). Additional reductions in BASDAI compared with placebo were 0.70 units with etanercept, 1.23 with

adalimumab, 1.85 with certolizumab pegol, and 2.67 units with infliximab. Additional BASFI reductions were 0.60 units with etanercept, 0.90 units with adalimumab, 1.90 units with certolizumab pegol and 2.24 units with infliximab. Infliximab appeared to be the most effective, but this trial was judged to have a high risk of bias.

4.14 When TNF-alpha inhibitors were considered as a class, with 1 treatment effect, the meta-analysis showed statistically significant improvements compared with placebo at 10 to 16 weeks for all outcomes (table 3). The Assessment Group reported that statistical heterogeneity was apparent in the analyses, and therefore the reliability of the pooled estimates, and their true relevance to people seen in clinical practice, is questionable. Estimates of the class effect of TNF-alpha inhibitors were consistently smaller in non-radiographic axial spondyloarthritis compared with those seen in ankylosing spondylitis trials (most noticeably for BASFI and BASDAI 50).

Table 3 Estimated class effect of TNF-alpha inhibitors compared with placebo in non-radiographic axial spondyloarthritis: meta-analysis of outcomes at 10 to 16 weeks (main analysis)

–	Outcome	95% CI
ASAS 20 (RR)	1.65	1.37 to 2.04
ASAS 40 (RR)	2.74	2.08 to 3.62
BASDAI 50 (RR)	2.31	1.76 to 3.10
BASDAI (additional reduction from baseline)	−1.32	−1.74 to −0.90
BASFI (additional reduction from baseline)	−0.99	−1.34 to −0.64
BASMI (additional reduction from baseline)	−0.15	−0.32 to 0.02
SF-36 PCS (additional reduction from baseline)	4.41	3.04 to 5.81
SF-36 MCS (additional reduction from baseline)	2.33	0.07 to 4.62

Abbreviations: ASAS, Assessment in Spondyloarthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; RR, relative risk; SF-36 MCS, Short Form 36 mental component summary; SF-36 PCS Short Form 36 physical component summary.

4.15 The Assessment Group did indirect comparisons of the TNF-alpha inhibitors. There were no statistically significant differences between the 5 TNF-alpha inhibitors for efficacy outcomes at 10 to 16 weeks.

4.16 Analysis of long-term efficacy results from open-label extension studies showed that, after 1 year of treatment, non-radiographic axial spondyloarthritis continues to respond well to TNF-alpha inhibitors in around half of people with the disease. This level of response is maintained up to 2 years with certolizumab pegol and up to 3 years with adalimumab. Mean change from baseline for BASDAI, BASFI and BASMI (if reported) were generally maintained at clinically meaningful levels during long-term follow-up (data available up to 1 year). However, the open-label extension studies produced less reliable data than the RCTs. Results may not reflect clinical practice, because some people continued treatment even though their disease did not respond to therapy (contrary to the UK marketing authorisations). The Assessment Group concluded that the long-term benefits of TNF-alpha inhibitors appear similar across treatments.

4.17 The Assessment Group did not identify any efficacy data for people with non-radiographic axial spondyloarthritis who had switched to a second or third TNF-alpha inhibitor.

Adverse events

4.18 The identified RCTs did not allow for a meaningful analysis of adverse events because of limitations in the number and size of RCTs and the short duration of the placebo-controlled periods. The Assessment Group evaluated adverse event rates from a Cochrane Review and from network meta-analysis of 9 biological interventions (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab) in adults with any disease, except HIV/AIDS. The Cochrane Review included 160 RCTs (including 48,676 people); 115 of these RCTs (72%) included the TNF-alpha inhibitors under consideration in this appraisal.

4.19 Analysis of the Cochrane Review showed that, as a group, TNF-alpha inhibitors are associated with significantly higher rates of serious infections, tuberculosis reactivation, non-melanoma skin cancer, total adverse events, and withdrawals

because of adverse events, when compared with control treatments in the short-term (median treatment duration of the RCTs was 6 months).

4.20 When individual TNF-alpha inhibitors were analysed separately, only infliximab and certolizumab pegol were associated with statistically significant increases in adverse events compared with control treatments:

- infliximab was associated with higher rates of total adverse events (number needed to harm [NNH] 13, 95% credible interval [CrI] 8 to 505) and withdrawals because of adverse events (NNH 10, 95% CrI 5 to 30)
- certolizumab pegol was associated with higher rates of serious infections (NNH 12, 95% CrI 4 to 79) and serious adverse events (NNH 18, 95% CrI 9 to 162).

4.21 Cancer risk was not analysed as part of the Cochrane Review. Because TNF-alpha inhibitors are known to have a possible association with cancer, the Assessment Group identified an individual patient-data meta-analysis (including 22,904 people from 74 RCTs) that assessed the cancer risk associated with 3 of the TNF-alpha inhibitors under consideration in this appraisal (adalimumab, etanercept and infliximab). When considering the class effect of the 3 TNF-alpha inhibitors, there was no increase in risk of cancers excluding non-melanoma skin cancer (RR 0.99, 95% confidence interval [CI] 0.61 to 1.68). However TNF-alpha inhibitors were associated with a doubling in the risk of non-melanoma skin cancer (RR 2.02, 95% CI 1.11 to 3.95).

Evidence from patient experts

4.22 Patient experts discussed the 2 conditions together, reporting that the key symptom is inflammatory back pain which becomes increasingly severe over time. Up to 25% of people with ankylosing spondylitis or non-radiographic axial spondyloarthritis eventually develop complete fusion of the spine, which leads to substantial disability. Patient experts noted that, because the conditions present at an early age when people are beginning their career (average age of onset is 24 years), disease progression leads to substantial loss in work productivity. One-third of people give up work before normal retirement age and another 15%

reduce or change their work because of their disease. Being unable to work has important consequences both for the individual and for their family; people with ankylosing spondylitis or non-radiographic axial spondyloarthritis are more likely to divorce or to never marry and women are less likely to have children. Many people with the conditions report depression and fatigue. Patient experts reported that, in addition to local spinal symptoms, 50% of people suffer from associated disorders elsewhere. For example, 40% experience eye inflammation, 16% develop psoriasis and 10% have inflammatory bowel disease. Patient experts also highlighted the issue of underdiagnosis – symptoms are often present for 7 to 10 years before a diagnosis is made.

4.23 Comments from patient experts indicated the outcome most important to people with axial spondyloarthritis was the prevention of further damage to their spine and joints. A reduction in pain and fatigue was also important. The patient experts stated that people having TNF-alpha inhibitors have reported substantial improvements in pain and stiffness, leading to improvements in mobility and an improved quality of life. People reported that they were able to independently manage activities of daily living that were previously problematic. However, patient experts estimated that 2 in 10 cases of axial spondyloarthritis do not respond to treatment with a TNF-alpha inhibitor. Based on previous NICE guidance, these people would not be offered an alternative TNF-alpha inhibitor. This knowledge leads to high levels of anxiety in people with axial spondyloarthritis. The option to switch to a second TNF-alpha inhibitor would reduce fears and anxiety. There is also anecdotal evidence suggesting that a second or third TNF-alpha inhibitor can be clinically effective if the first has failed.

4.24 The patient experts reported that when people were asked about infliximab specifically, some people preferred its mode of administration (an infusion administered by a healthcare professional) to the method of self-injection. This might benefit people with memory problems, learning disabilities, dexterity problems, or a fear of needles. However, some people were worried about the potential for postponed appointments (leading to a return of symptoms) and the need to take time off work and the need to travel for treatment with infliximab.

Cost effectiveness

Published evidence

4.25 The Assessment Group's systematic review of cost-effectiveness evidence identified 5 published economic evaluations of TNF-alpha inhibitors in patients with ankylosing spondylitis. No published economic evaluations were identified for patients with non-radiographic axial spondyloarthritis. The Assessment Group considered that the published models lacked evidence-based justifications for parameter estimates and structural assumptions.

Company submissions

4.26 For ankylosing spondylitis, the companies compared the 5 TNF-alpha inhibitors that have a marketing authorisation for this indication (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) with each other, and with conventional care. For non-radiographic axial spondyloarthritis, the companies compared the 3 TNF-alpha inhibitors that have a marketing authorisation in this indication (adalimumab, certolizumab pegol and etanercept) with each other and with conventional therapy (except for AbbVie, which did not include etanercept in its model). All evaluations adopted an NHS perspective. Costs and benefits in all cases were discounted at 3.5%.

4.27 The companies used a lifetime horizon for their models, except AbbVie (adalimumab) which used a 40-year time horizon. Based on recommendations in NICE's technology appraisal guidance on adalimumab, etanercept and infliximab for ankylosing spondylitis, all models included response criteria to decide whether TNF-alpha inhibitors were continued or stopped. The criteria were ASAS 20, ASAS 40 or BASDAI 50 at week 12, except for UCB Pharma which used response criteria at week 24, in its base-case model for the ankylosing spondylitis population. In common with previously published models, the models were based on the estimation of BASDAI and BASFI scores over time. All models assumed that, after initial improvements in BASDAI for people whose disease responds to treatment, BASDAI scores remain relatively constant over the longer term. However, there were differences in assumptions about long-term disease

progression (that is, changes in physical function measured by BASFI) and the rebound effect after treatment withdrawal (in patients whose disease initially responded but then stopped responding to therapy). The models assumed 1 of 2 scenarios; 'optimistic' or 'pessimistic'. The optimistic scenario assumed an ongoing benefit of TNF-alpha inhibitors after withdrawal (known as 'rebound equal to gain' or 'rebound to baseline'). In this scenario, physical function (measured by BASFI) deteriorates ('rebounds') to the patient's baseline level. The pessimistic scenario assumed a greater deterioration in physical function after treatment withdrawal, to the level that it would have been if the disease had not initially responded to therapy (known as 'rebound to natural history' or 'rebound to conventional care'). In both scenarios, the subsequent trajectory of disease progression after rebound (measured by BASFI) mirrors the natural history of the disease. Differences in assumptions are presented in table 4 and table 5, along with other key structural assumptions.

Table 4 Model structure and key assumptions: ankylosing spondylitis

Parameter	Infliximab, Golimumab	Adalimumab	Certolizumab pegol	Etanercept
Model type	Decision tree followed by Markov model	Markov model	Decision tree followed by Markov model	Patient-level simulation model
Response criteria (12 or 24 weeks)	BASDAI 50 response	ASAS 20 response	ASAS 20 response	BASDAI 50 response
Response criteria justification	GO-RAISE outcome	ATLAS primary endpoint	RAPID-axSpA primary endpoint	NICE definition of response (TA143)
Annual rate of withdrawal (long-term)	6.1% (GO-RAISE). Applied to all TNF-alpha inhibitors in the model	<15.0% on treatment at year 40 (ATLAS). Applied to all TNF-alpha inhibitors in the model	7.0% (NICE TA143). Applied to all TNF-alpha inhibitors in the model	11.0% for etanercept

Parameter	Infliximab, Golimumab	Adalimumab	Certolizumab pegol	Etanercept
BASFI progression: disease responds to TNF-alpha inhibitor 'responders'	Constant after week 108; 0.035 after week 256	Constant after week 260	Constant after week 24	Constant after week 48
BASFI progression: TNF-alpha inhibitor 'non-responders'	0.070	0.056	0.070	0.070
BASFI progression: Conventional care	0.070 after week 24	0.056	0.070	0.070 after week 12
Rebound assumption	Rebound to baseline (6 months)	Rebound to baseline (immediately)	Rebound to conventional therapy (6 months)	Rebound to baseline (6 months)

Abbreviations: ASAS, Assessment in Spondyloarthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; MSD, Merck Sharp & Dohme; TA, technology appraisal; TNF, tumour necrosis factor.

Table 5 Model structure and key assumptions: non-radiographic axial spondyloarthritis

Parameter	Adalimumab	Certolizumab pegol	Etanercept
Model type	Markov model	Decision tree followed by Markov model	Patient-level simulation model
Response criteria (12 or 24 weeks)	ASAS 40 response	ASAS 20 response	BASDAI 50 response
Response criteria justification	ABILITY-1 primary endpoint	RAPID-axSpA primary endpoint	NICE definition of response (TA143)

Parameter	Adalimumab	Certolizumab pegol	Etanercept
Annual rate of withdrawal (long-term)	<10% on treatment at year 40 (ATLAS)	7% (NICE technology appraisal guidance on adalimumab, etanercept and infliximab for ankylosing spondylitis)	5% for etanercept
BASFI progression: TNF-alpha inhibitor 'responders'	Constant after week 140	Constant after week 12	Constant after week 48
BASFI progression: TNF-alpha inhibitor 'non-responders'	0.084 (ABILITY-1 study)	0.070 (Kobelt 2007)	Constant: 0.070 (Kobelt 2007)
BASFI progression: Conventional care	0.084	0.070	0.070 after week 12
Rebound assumption	Rebound to baseline (immediately)	Rebound to conventional therapy (6 months)	Rebound to baseline (6 months)

Abbreviations: ASAS, Assessment in Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; TA, technology appraisal; TNF, tumour necrosis factor.

Comparison of company models

4.28 A comparison of the base-case incremental cost-effectiveness ratio (ICER) estimates compared with conventional therapy submitted by each company is provided in table 6 (ankylosing spondylitis) and table 7 (non-radiographic axial spondyloarthritis).

Table 6 Ankylosing spondylitis: comparisons of company ICER estimates (£ per quality-adjusted life year [QALY] gained) compared with conventional therapy

–	AbbVie (adalimumab)	UCB Pharma	Pfizer (etanercept)	MSD (golimumab, infliximab)
Conventional care	-	-	-	-

–	AbbVie (adalimumab)	UCB Pharma	Pfizer (etanercept)	MSD (golimumab, infliximab)
Adalimumab	16,391	19,932	20,909	19,275
Certolizumab pegol	17,067.Based on list price for certolizumab pegol	16,647. Based on patient access scheme for certolizumab pegol	19,586.Based on patient access scheme for certolizumab pegol	19,401[2]
Etanercept	16,897	19,272	20,938	21,972
Golimumab	16,535	19,049	21,288	19,070
Infliximab	44,448	42,671	37,741	42,532

Abbreviations: MSD, Merck Sharp & Dohme.

Table 7 Non-radiographic axial spondyloarthritis: comparisons of company ICER estimates (£ per quality-adjusted life year [QALY] gained) compared with conventional therapy

–	AbbVie (adalimumab)	UCB Pharma	Pfizer (etanercept)
Conventional care	-	-	-
Adalimumab	13,228	30,370	23,242
Certolizumab pegol	12,866. Based on list price for certolizumab pegol	15,615. Based on patient access scheme for certolizumab pegol	23,575.Based on patient access scheme for certolizumab pegol
Etanercept	Not Assessed	50,692	23,195

4.29 The Assessment Group commented that, in general, the companies submitted good quality models. Despite the different model structures and assumptions used across the company submissions, similar ICERs were reported for each of the TNF-alpha inhibitors compared with conventional care in ankylosing spondylitis. There were greater differences between company submissions in the ICERs reported for non-radiographic axial spondyloarthritis'. The Assessment Group suggested that the variation in ICER estimates reported across the submissions (both within and between populations) might be explained by differences in the following parameters and underlying assumptions:

- the response criteria and time when response was measured
- the magnitude of improvement in outcomes and the time when these were assumed to 'level off' (that is, plateau)
- the underlying rate of disease progression, measured by change in BASFI scores, without treatment ('natural history' of disease) and the impact of TNF-alpha inhibitors on this rate
- disease progression after treatment stopped (the 'rebound' assumption) and the timing of this.

4.30 Although there was consistency across the companies' ICER estimates for the ankylosing spondylitis population, the Assessment Group considered them (and the ICERs reported for people with non-radiographic axial spondyloarthritis) to be both speculative and uncertain. The uncertainty is because of unresolved issues with parameter estimates and structural assumptions used in published cost-effectiveness evaluations (highlighted in the Assessment Group's review). For example, several company models used data from open-label extension studies without any formal consideration of the selection bias inherent in these studies. The Assessment Group was also concerned about the appropriateness of the sources of natural history data, and subsequent assumptions made about the trajectories of BASDAI and BASFI progression. Related to this are assumptions about the effect of TNF-alpha inhibitors on disease progression, and a lack of consensus on whether TNF-alpha inhibitors are primarily symptom-control treatments or whether they are also disease modifiers. The Assessment Group noted that identical assumptions for the impact of treatment on progression were applied across both populations, without consideration of how generalisable these assumptions were. Finally, the Assessment Group suggested that BASDAI and BASFI may not be the most appropriate conceptual basis for modelling progression of these diseases. But, in the absence of data linking other disease measures to costs and utilities, it concluded that there were no other options.

Sequential treatment

4.31 The Assessment Group did not believe that the company submissions provided a

robust basis for informing the cost effectiveness of intermittent and sequential use of TNF-alpha inhibitors. Only Pfizer submitted evidence for the cost effectiveness of sequential treatment. In its base-case analysis, only people who stopped treatment because of adverse events were eligible to receive a second TNF-alpha inhibitor. The model assumed that the second treatment had equal efficacy to the first. In a sensitivity analysis, people who stopped treatment because of loss of response also switched to a second TNF-alpha inhibitor, which was assumed to have a reduced effect. In the sensitivity analysis, pairwise comparison of the TNF-alpha inhibitors with conventional care showed that, in a mixed population of people who had and who had not previously received TNF-alpha inhibitors, the ICERs for treatment were about £1,000 higher than the ICERs for a population only of people who had not previously received treatment (for all treatments except infliximab). This was the case for both ankylosing spondylitis and non-radiographic axial spondyloarthritis. Excluding infliximab, the ICERs for the other TNF-alpha inhibitors in ankylosing spondylitis were similar (ranging from £21,823 to £22,641 per quality-adjusted life year [QALY] gained). The ICER for infliximab for the mixed population was £35,766 per QALY gained (lower than the ICER for infliximab for a population of people who had not received treatment). The ICERs for the 3 treatments for non-radiographic axial spondyloarthritis ranged from £23,877 to £24,041 per QALY gained. The company used evidence from the DANBIO patient registry to estimate the efficacy of the second TNF-alpha inhibitor. The Assessment Group commented that registries are unreliable because of their selection bias. The company also stated that the results of this analysis should be interpreted with caution because of the lack of robust clinical data showing the efficacy of sequential treatment.

Assessment Group's model

4.32 The Assessment Group developed a de novo economic model to assess the cost effectiveness of all 5 TNF-alpha inhibitors that have a marketing authorisation for ankylosing spondylitis and the 3 that are licensed for non-radiographic axial spondyloarthritis. The Assessment Group developed a cohort model in the form of a modified decision tree. The model used a lifetime horizon, assuming that patients enter the model at the age of 40 years and have an average body weight of 73 kg. BASDAI 50 response at 12 weeks determined whether patients continued having a TNF-alpha inhibitor or withdrew from treatment. For those

whose disease responded, there was an ongoing risk of treatment withdrawal at any time point. Patients who stopped treatment (at 12 weeks or later) were assumed to move on to conventional care. The analysis was done from the perspective of the NHS and personal social services, and costs and health effects were discounted at an annual rate of 3.5%. The mean costs and QALYs reported are derived from probabilistic sensitivity analysis (that is, produced by varying the input parameters simultaneously with values from a probability distribution).

4.33 To address some of the uncertainties identified in published economic evaluations and company submissions, and to generate more appropriate parameter estimates (and associated uncertainties) for its de novo model, the Assessment Group performed an extended evidence synthesis of the available clinical data. The evidence synthesis was used to estimate baseline BASDAI/BASFI scores, the effect of treatment on these scores, and the probability of a response (BASDAI 50) at 12 weeks. The Assessment Group also used a new approach to model long-term disease progression and the impact of treatment on the natural history of disease, by relating the assumptions more explicitly to the existing clinical data for TNF-alpha inhibitors. Specifically, the Assessment Group accounted for the independent effects of symptomatic improvements (that is, a reduction in disease activity according to BASDAI) on BASFI scores. It also considered the effect of changes in radiographic progression (measured by mSASSS) on BASFI. Because of these analyses, the model assumed that patients who continued to have, and whose disease responded to ('responders'), a TNF-alpha inhibitor after week 12 had a slower progression rate (according to BASFI scores) compared with the natural history of the disease (this effect was delayed until year 4). For 'responders' who subsequently stopped taking TNF-alpha inhibitors, there was some rebound in BASFI and BASDAI scores (this is also relevant for patients who stop at 12 weeks). Because trial data could not accurately characterise the extent of this rebound, the Assessment Group presented 2 scenarios in their base case; 1 assuming rebound to baseline and 1 assuming rebound to natural history (representing the best-case and worst-case scenarios respectively). The Assessment Group's model used different baseline BASDAI/BASFI scores for 'responders' and for patients whose disease did not respond ('non-responders'). Therefore, in the rebound to baseline scenario, 'responders' and 'non-responders' reverted to different baseline scores after treatment was stopped. This assumption was based on results from the

extended synthesis, which estimated that 'non-responders' had higher baseline BASDAI and BASFI scores than 'responders' (that is, response is unlikely to be independent of baseline patient characteristics).

4.34 Health-related quality of life was estimated using BASDAI and BASFI data, using the approach submitted by Pfizer. Separate algorithms were used for each population, using data from the 1031 study and the 314-EU study (both mapped to EQ-5D).

4.35 The only adverse-event costs included in the model were serious infections and tuberculosis reactivation. All other costs were assumed to vary according to the BASFI score (data were derived from the OASIS database). The Assessment Group's model used both the list price for certolizumab pegol and the patient access scheme, so that the list price ICERs could be considered until the patient access scheme is agreed by the Department of Health.

4.36 The Assessment Group did 6 sensitivity analyses:

- **Scenario 1** assumed no placebo effect; that is, no patients having conventional care had a BASDAI 50 response at week 12. By contrast, the base-case model incorporated a probability of response to conventional care at 12 weeks.
- **Scenario 2** reduced the difference in baseline BASDAI/BASFI scores between 'responders' and 'non-responders'. As in the base case, a difference still exists (conditional on response). But while the base case used estimates from the Assessment Group's extended synthesis, the sensitivity analysis was informed by data from company submissions. This scenario also used data pooled from company submissions (instead of the extended synthesis) to estimate the change in BASDAI and BASFI scores for 'responder's and 'non-responders'.
- **Scenario 3** assumed that TNF-alpha inhibitors have no effect on BASFI progression (in the base case, BASFI progression is slowed in 'responders').
- **Scenario 4** assumed that the treatment effect of TNF-alpha inhibitors (measured by BASFI) was reached immediately. By contrast, in the base-case model, disease modification was delayed until year 4.

- **Scenario 5** mapped utilities using a linear model (consistent with previous NICE technology appraisal guidance on adalimumab, etanercept and infliximab and on golimumab for treating ankylosing spondylitis). The base case used a non-linear mapping algorithm.
- **Scenario 6** used results from ankylosing spondylitis trials in the model for non-radiographic axial spondyloarthritis.

4.37 In both the base-case model and the sensitivity analyses, the Assessment Group assumed a class effect of TNF-alpha inhibitors (that is, the QALYs gained are the same for each) based on their review of the clinical evidence. Therefore, the difference in the ICERs between the individual TNF-alpha inhibitors is driven entirely by different acquisition and administration costs. In a fully incremental comparison of cost effectiveness, using the class effect assumption, the TNF-alpha inhibitor with the lowest cost would dominate the other treatments (that is, provide the same QALYs at a lower cost). Therefore, the Assessment Group presented pairwise ICERs comparing each TNF-alpha inhibitor with conventional therapy.

Results for patients with ankylosing spondylitis

4.38 In the rebound to baseline scenario (table 8), pairwise comparison of the TNF-alpha inhibitors with conventional care showed that infliximab had the highest ICER (£40,576 per QALY gained) and the lowest probability of being cost effective at a £20,000 and £30,000 per QALY threshold (0% and 9% respectively). The ICER for infliximab using the biosimilar price was £36,751 per QALY gained. Excluding infliximab, the ICERs of the other TNF-alpha inhibitors were similar, ranging from £19,240 (certolizumab pegol with the PAS) to £21,577 (etanercept). At a maximum acceptable ICER of £20,000 per QALY gained, certolizumab pegol with the patient access scheme had a 55% probability of being cost effective compared with conventional therapy. Its probability of being cost effective compared with conventional therapy at a maximum acceptable ICER of £30,000 per QALY gained was about 90%.

Table 8 Base-case results for ankylosing spondylitis: rebound to baseline

–	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	110,821	7.245	-	-	-
Certolizumab pegol with the PAS	128,485	8.163	17,665	0.918	19,240
Golimumab	130,173	8.163	19,352	0.918	21,079
Adalimumab	130,257	8.163	19,436	0.918	21,170
Etanercept	130,630	8.163	19,810	0.918	21,577
Infliximab	148,073	8.163	37,252	0.918	40,576

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

4.39 In the rebound to natural history scenario (table 9), the ICERs for the TNF-alpha inhibitors varied between £33,762 (certolizumab pegol with the patient access scheme) and £66,529 (infliximab) per additional QALY gained, compared with conventional care. The ICER using the biosimilar price for infliximab was £60,222 per QALY gained. At a maximum acceptable ICER of £20,000 per QALY gained, certolizumab pegol with the patient access scheme had only a 4% probability of being cost effective compared with conventional therapy. This probability rose to 40% at a maximum acceptable ICER of £30,000 per QALY gained. As before, infliximab had the lowest probability of being cost effective (0% likelihood at both thresholds).

Table 9 Base-case results for ankylosing spondylitis: rebound to natural history

–	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	109,933	7.265	-	-	-
Certolizumab pegol with the PAS	130,277	7.867	20,344	0.603	33,762
Golimumab	131,960	7.867	22,027	0.603	36,554
Adalimumab	132,045	7.867	22,111	0.603	36,695
Etanercept	132,423	7.867	22,489	0.603	37,322

–	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Infliximab	150,022	7.867	40,088	0.603	66,529

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

4.40 The ICER estimates appeared to remain relatively stable (compared with the base-case results) across most of the 6 sensitivity analyses. The exception to this was scenario 2, which used company data to inform the baseline BASDAI/BASFI scores (conditional on response) and to estimate the change in BASDAI and BASFI scores for 'responders' and 'non-responders'. When the company data were used, the ICER estimates became more favourable towards the TNF-alpha inhibitors (table 10), driven by smaller differences between the baseline scores of 'responders' and 'non-responders'.

Table 10 Results of the Assessment Group's sensitivity analysis (scenario 2) for ankylosing spondylitis (£ per QALY gained)

–	Incremental cost-effectiveness ratio (ICER)	Incremental cost-effectiveness ratio (ICER)
Certolizumab pegol with PAS	14,803	26,348
Golimumab	16,451	28,892
Adalimumab	16,535	29,018
Etanercept	16,907	29,580
Infliximab	34,246	55,842

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme.

Results for patients with non-radiographic axial spondyloarthritis

4.41 In the rebound-to-baseline scenario (table 11), the ICERs of the alternative TNF-alpha inhibitors ranged from £28,247 (certolizumab pegol with the patient access scheme) to £29,784 (etanercept) per QALY gained, compared with conventional care. The probability that certolizumab pegol with the patient access scheme was more cost effective than conventional care alone was 14% at

a maximum acceptable ICER of £20,000 per QALY threshold and 59% at a maximum acceptable ICER of £30,000 per QALY threshold.

Table 11 Base-case results for non-radiographic axial spondyloarthritis: rebound to baseline

–	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER(£/QALY)
Conventional therapy	89,493	9.956	-	-	-
Certolizumab pegol with PAS	128,911	11.351	39,418	1.395	28,247
Adalimumab	130,316	11.351	40,823	1.395	29,253
Etanercept	131,057	11.351	41,563	1.395	29,784

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

4.42 In the rebound-to-natural-history scenario (table 12), the ICER of the alternative TNF-alpha inhibitors varied between £32,528 (certolizumab pegol with the patient access scheme) to £34,232 per additional QALY (etanercept). At a maximum acceptable ICER of £20,000 per QALY gained, certolizumab pegol with the patient access scheme had a 6% probability of being cost effective compared with conventional therapy. The probability of certolizumab pegol with a patient access scheme being cost effective compared with conventional therapy at a maximum acceptable ICER of £30,000 per QALY gained was about 43%.

Table 12 Base-case results for non-radiographic axial spondyloarthritis: rebound to natural history

–	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	89,395	9.880	-	-	-
Certolizumab pegol with PAS	130,341	11.139	40,946	1.259	32,528
Adalimumab	131,740	11.139	42,346	1.259	33,639
Etanercept	132,486	11.139	43,091	1.259	34,232

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

4.43 The ICER estimates remained relatively stable (compared with the base-case results) across the 6 sensitivity analyses. Scenario 2 showed the largest variation compared with the base-case analysis. ICER estimates became more favourable towards the TNF-alpha inhibitors (table 13), driven by smaller differences between the baseline scores of 'responders' and 'non-responders'.

Table 13 Results of the Assessment Group's sensitivity analysis' (scenario 2) for non-radiographic axial spondyloarthritis (£ per QALY)

–	Incremental cost-effectiveness ratio Rebound to baseline	Incremental cost-effectiveness ratio Rebound to natural history
Certolizumab pegol with patient access scheme	21,757	25,326
Adalimumab	22,593	26,287
Etanercept	23,036	26,784

4.44 The Assessment Group listed the following as the main limitations in its model:

- BASDAI and BASFI may not be the most appropriate tools for modelling disease progression, but they were used because of a lack of data linking costs and QALYs to other disease measures
- uncertainty remains in long-term projections of BASDAI and BASFI scores
- there are potential benefits that have not been formally captured and quantified, such as potential impact on productivity costs and benefits that TNF-alpha inhibitors may confer for extra-articular manifestations
- the model could not address important clinical questions on the sequential use of TNF-alpha inhibitors
- the model is based on an assumption that 12-week continuation rules are adhered to in clinical practice, which does not necessarily reflect how TNF-alpha inhibitors are currently used within the NHS.

4.45 The Assessment Group acknowledged that BASDAI and BASFI may not be the most appropriate measures to use in the model. However, it considered that its approach captured the potential impact of TNF-alpha inhibitors on long-term disease progression (BASFI changes) more explicitly than existing models. The de

novo model included changes in different clinical/biological processes (in addition to disease activity according to BASDAI) that independently affect BASFI. The Assessment Group considered that the effect of symptomatic improvements (that is, changes in BASDAI scores) on BASFI was captured in the conditional scores applied to 'responders'. In addition, because long-term BASDAI was assumed to be constant after the short-term response period, long-term changes in BASFI were modelled as a function of mSASSS scores.

Evidence submitted following consultation

4.46 Following consultation on the preliminary guidance, the companies that market biosimilar infliximab presented updated economic analyses using a range of prices for infliximab to reflect the tendering process that was ongoing at the time of the consultation. Ranges, rather than single prices, were necessary because the process is regional rather than national and may differ between organisations. After the Committee meeting at which these analyses were discussed, NICE was able to confirm with the Commercial Medicines Unit that the tendering process was complete and that the prices presented in the companies' submissions were now available within the NHS. The Assessment Group then recalculated their base-case ICERs for infliximab in ankylosing spondylitis using an acquisition cost of infliximab to reflect the highest price the NHS would need to pay for infliximab (that is, the upper end of the range of acquisition costs for the cheapest product) and the Committee's preferred infusion cost (see section 4.65). Because the contract prices resulting from the tendering process are commercially confidential, the results of this analysis are not presented here (because this could allow the contract prices to be estimated from the ICERs).

Consideration of the evidence

4.47 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of TNF-alpha inhibitors, having considered evidence on the nature of ankylosing spondylitis and non-radiographic axial spondyloarthritis and the value placed on the benefits of TNF-alpha inhibitors by people with the conditions, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management

4.48 The Committee discussed the diagnosis of ankylosing spondylitis or non-radiographic axial spondyloarthritis. It heard that differentiation between the two is based on radiological changes on X-rays. The Committee understood that to diagnose ankylosing spondylitis, definitive radiographic change on X-ray is needed. The Committee heard from the clinical experts that diagnosing non-radiographic axial spondyloarthritis is more complex. People who have clinical signs and symptoms of axial spondyloarthritis together with MRI changes showing inflammation are the easiest to diagnose, although sometimes repeat MRI scanning may be needed to detect changes. A smaller number do not have MRI changes but have other objective markers of inflammation (that is, elevated levels of C-reactive protein). In general, clinicians are much less confident of the diagnosis based on symptoms alone, in the absence of MRI or C-reactive protein changes. Clinical and patient experts explained the importance of early diagnosis and treatment in order to prevent or delay progressive and irreversible damage, which could ultimately cause people to need a wheelchair or be unable to get out of bed because of the severity of their physical disability. They noted that delayed diagnosis is common, and that the mean time from the development of symptoms to diagnosis in the UK is about 8.4 years. The Committee heard that reasons for delayed diagnosis include a low awareness of the conditions in the general population; a presenting symptom that is non-specific (for example, back pain); lack of a clear clinical pathway; and lack of follow-up for people who do not present with X-ray changes. The Committee also heard that although MRI scanning shows inflammation before it becomes visible on X-ray, accurate diagnosis with MRI needs particular scanning techniques and appropriate specialist interpretation.

4.49 The Committee explored the differences, and relationship between ankylosing spondylitis and non-radiographic axial spondyloarthritis. It heard from the patient and clinical experts that these are 2 distinguishable conditions within a single spectrum of disease. Clinical experts suggested that some people with non-radiographic axial spondyloarthritis will develop ankylosing spondylitis (about 10% over 2 years and 50% over 10 years). The Committee heard that it is difficult to predict which people with non-radiographic axial spondyloarthritis will progress, and at what rate it would happen.

4.50 The Committee discussed the impact on quality of life of both conditions. The Committee understood from both the clinical and patient experts that these are chronic, progressive conditions associated with pain, stiffness and increasing spinal and other joint damage. It noted that there may be extra-articular manifestations of disease such as uveitis, colitis, psoriasis, and cardiovascular problems, as well as symptoms such as depression, fatigue and lack of sleep. The Committee was aware that these conditions have a significant impact on a person's mobility, social life, employment, mental health and overall quality of life. The Committee understood that the families of people with these conditions may also be substantially impacted.

4.51 The Committee discussed the current management of ankylosing spondylitis. The Committee heard that symptoms will not be controlled by NSAIDs in 40% of people with ankylosing spondylitis, and others will be not be able to tolerate NSAIDs. The Committee noted that adalimumab, etanercept and golimumab were 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 on adalimumab, etanercept and infliximab and golimumab for treating ankylosing spondylitis). The Committee understood that access to other TNF-alpha inhibitors, such as certolizumab pegol and infliximab, would allow patients and clinicians a greater choice of treatment options. The Committee heard from patient experts that TNF-alpha inhibitors had completely changed some people's lives by restoring mobility and reducing pain, and could allow people to continue working and fulfilling parental and carer duties. A patient expert stated that his TNF-alpha-inhibitor treatment had also stopped flare-ups of uveitis. The Committee heard from the clinical experts that individual TNF-alpha inhibitors have different effects on extra-articular manifestations and so the choice of TNF-alpha inhibitor in clinical practice is based on individual patient characteristics. The Committee also heard that the TNF-alpha inhibitors have different modes of administration; adalimumab, certolizumab pegol, etanercept and golimumab are given by subcutaneous injection and infliximab is given by infusion in hospital. The Committee heard from the patient experts that infliximab may be a preferable treatment option for patients who may have difficulty with or who are unable to self-inject. It also heard that infliximab may also be more suitable for people who need more time between treatments to allow them to travel, although the Committee noted that golimumab is given only every

4 weeks. The Committee understood the importance of TNF-alpha inhibitors for treating ankylosing spondylitis.

4.52 The Committee considered the use of TNF-alpha inhibitors in people with non-radiographic axial spondyloarthritis. The patient and clinical experts emphasised that there is a misconception that this condition is less severe than ankylosing spondylitis. They explained that both conditions result in the same level of pain, reduced function and poor quality of life. People severely affected by the condition found it hard to understand why they had to wait for changes to be visible on X-rays before being eligible for treatment with TNF-alpha inhibitors.The Committee noted that adalimumab, certolizumab pegol and etanercept have UK marketing authorisations for use in people with non-radiographic axial spondyloarthritis. It understood that golimumab had recently been given regulatory approval for this indication, but was not included in this appraisal because the positive Committee for Medicinal Products for Human Use opinion was received at a late stage in the appraisal process. Although there are 4 TNF-alpha inhibitors available for this indication, the Committee heard that there was extreme variability in access to TNF-alpha inhibitors across the country, and that access was based on individual funding requests. The Committee understood that there was clinical support for the use of TNF-alpha inhibitors in people with non-radiographic axial spondyloarthritis, whose disease is not controlled by, or who cannot tolerate, NSAIDs. The clinical experts stated that early treatment with TNF-alpha inhibitors could prevent spinal damage in these people. The clinical experts clarified the diagnosis of non-radiographic axial spondyloarthritis, and further divided people with symptoms of the condition into 3 groups: people with MRI changes; those with no MRI changes but elevated C-reactive protein levels; and those without MRI changes and without elevated C-reactive protein. The experts suggested that people with symptoms of non-radiographic axial spondyloarthritis, but without objective signs of inflammation are less likely to benefit from TNF-alpha-inhibitor treatment. The Committee understood that TNF-alpha inhibitors are not indicated for people with symptoms of non-radiographic axial spondyloarthritis, but without objective signs of inflammation and concluded that it could not make recommendations for treatment with TNF-alpha inhibitors in this group of patients.

4.53 The Committee discussed the response criteria used to determine whether

TNF-alpha-inhibitor treatment is continued in clinical practice. It heard from clinical experts that in UK clinical practice, response to TNF-alpha-inhibitor treatment is usually assessed after 3 months. They defined an adequate response to treatment as an improvement in BASDAI score of at least 50%, or of at least 2 units. The experts explained that, in some people, the disease will not show a response to treatment until 6 months, but that most responses or partial responses occur within 3 months. The Committee heard from the patient expert that his disease responded to treatment after only 8 weeks. The Committee also heard that the probability of response to TNF-alpha inhibitors is higher in clinical practice than in clinical trials (about an 85% response rate in practice compared with 50% to 60% in clinical trials). The clinical experts suggested that this could, in part, be because of the more restrictive definition of response used in clinical trials compared with clinical practice. The Committee concluded that an improvement of 2 units in the BASDAI score represented a meaningful and clinically significant benefit, independent of the baseline BASDAI score.

4.54 The Committee heard from the clinical experts that, in people who cannot tolerate a first TNF-alpha inhibitor or have adverse reactions, the disease is no less likely to respond to an alternative agent. People whose condition either does not respond to a first TNF-alpha inhibitor, or relapses after an initial response, are also likely to benefit from an alternative TNF-alpha inhibitor. The experts stated that the number of patients with ankylosing spondylitis or non-radiographic axial spondyloarthritis needing a subsequent TNF-alpha inhibitor is likely to be relatively small (around 6000), and may be related to differences in the drugs' mechanisms of action of or the development of antibodies. The Committee noted that switching between TNF-alpha inhibitors was not recommended in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab and golimumab for treating ankylosing spondylitis, except when intolerance to the first agent occurs in the first 3 months of treatment, before the assessment of response. For treatment switching after failure of a first TNF-alpha inhibitor, the patient expert commented that stopping TNF-alpha-inhibitor treatment after loss of response would mean returning to reliance on NSAID therapy, which has already been shown to provide inadequate symptom control, and is associated with long-term adverse effects. The Committee also noted that some patients are unable to take NSAIDs. The clinical and patient experts stated that the inability to switch agents results in many patients remaining on their sub-optimal TNF-alpha inhibitor indefinitely because of the lack of access to an

alternative more effective option. They suggested that it was preferable to switch to another agent at the same cost rather than continue with a less effective one. The patient experts emphasised that patients currently feel under extreme pressure to make the right first choice, knowing that they will not have the opportunity to try an alternative TNF-alpha inhibitor if their disease fails to respond to the first, or if it responds but subsequently gets worse again. The Committee acknowledged that predicting a disease response in advance was not possible, and that this could have a major impact on a lifelong condition. The Committee concluded that there was a clinical need for subsequent TNF-alpha inhibitor treatments.

Clinical effectiveness

4.55 The Committee considered the clinical-effectiveness evidence for each condition separately. The Committee agreed that the trials in ankylosing spondylitis were generalisable to clinical practice in the UK but noted substantial heterogeneity in the baseline characteristics in the trials of non-radiographic axial spondyloarthritis (such as variation in levels of C-reactive protein and the proportion of patients with MRI changes). The Committee heard from the clinical experts that the trial patient populations generally reflected the patients seen in UK clinical practice, although expressing some reservations about the inclusion of people without objective signs of inflammation, for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations. The Committee concluded that the trials were generalisable to the NHS.

4.56 The Committee discussed the results of the Assessment Group's meta-analysis for each condition. The Committee noted that all the TNF-alpha inhibitors showed a benefit compared with placebo at 10 to 16 weeks in both conditions. The Committee noted that infliximab appeared to be more effective at 12 weeks than other TNF-alpha inhibitors in ankylosing spondylitis, but questioned whether this benefit was sustained long-term. The Committee considered the results of the Giardina et al. trial (see section 4.8) and agreed that, on balance, there was not enough evidence to indicate that infliximab was more effective in the longer term than the other TNF-alpha inhibitors. The Committee concluded that TNF-alpha inhibitors were clinically effective compared with placebo and, given the lack of difference in effect between them, they should be considered as a class with

broadly similar, even if not completely identical, effects.

4.57 The Committee questioned whether the efficacy of TNF-alpha inhibitors was the same in both conditions. The Committee noted that the class effect results for TNF-alpha inhibitors were less favourable in non-radiographic axial spondyloarthritis compared with ankylosing spondylitis (except for outcomes measured on the health-related quality of life instrument: SF-36). The Committee heard from the clinical experts that they would not expect a differential response to treatment in the two conditions. Clinical experts stated that their limited clinical experience of TNF-alpha inhibitors in non-radiographic axial spondyloarthritis suggested that the magnitude of response was the same in both conditions. The Committee noted comments from the Assessment Group that heterogeneity across the trials of non-radiographic axial spondyloarthritis may have confounded the outcomes for TNF-alpha inhibitors. The Committee heard from the clinical experts that these trials included some people who were less likely to benefit from TNF-alpha inhibitors (people without objective signs of inflammation such as MRI changes and elevated C-reactive protein, for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations; see sections 4.48, 4.52 and 4.55). The Committee noted that clear guidelines for the diagnosis of non-radiographic axial spondyloarthritis would be helpful to identify patients who are more or less likely to benefit from TNF-alpha-inhibitor treatment. The Committee agreed that the clinical trials may have underestimated the benefit of TNF-alpha inhibitors in non-radiographic axial spondyloarthritis. The Committee concluded that people with non-radiographic axial spondyloarthritis are likely to achieve a similar benefit from TNF-alpha inhibitors as people with ankylosing spondylitis.

4.58 The Committee discussed whether there were any differences between the TNF-alpha inhibitors and heard from clinical experts that TNF-alpha inhibitors are well tolerated in both conditions, and that people rarely stop treatment because of adverse events (see section 4.54). The Committee noted comments from experts that there are differences between the TNF-alpha inhibitors in their effects on extra-articular manifestations (see section 4.51). The Committee heard from the clinical experts that in clinical practice the choice of TNF-alpha inhibitor is based on individual patient characteristics. The Committee concluded that TNF-alpha inhibitors are relatively well tolerated and that the clinical characteristics of the patient, particularly any extra-articular manifestations of

the disease, would need to be considered when choosing a TNF-alpha inhibitor.

4.59 The Committee considered the clinical evidence for treatment with a second or third TNF-alpha inhibitor for a person whose disease does not respond or stops responding to treatment (sequential treatment). The Committee noted the absence of randomised controlled trial data, but noted data from the DANBIO registry for ankylosing spondylitis and comments received on the appraisal consultation document identifying other registries and studies, including ATTRA, NOR-DMARD, RAPID-axSpA and RHAPSODY. It agreed that, despite a decrease in response rates for each subsequent treatment, sequential treatment with TNF-alpha inhibitors can be beneficial in ankylosing spondylitis. The Committee also noted consultation comments from a patient and carer group stating that a survey of 864 people with ankylosing spondylitis or non-radiographic axial-spondyloarthritis showed that 26% of those surveyed had received at least 1 other TNF-alpha inhibitor (about half of these because of adverse reactions and half because of a loss or lack of response); 79% of these people considered that switching had provided a moderate (11%) to large benefit (68%). The Committee also noted consultation comments stating that other appraisals, such as NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for psoriatic arthritis, had not placed a restriction on subsequent TNF-alpha-inhibitor use. However, the Committee was concerned that that there was very little evidence on sequential use, and was uncertain about the true magnitude of the benefit in ankylosing spondylitis. What evidence there was did not show a convincing differential effect, related to the reason for switching. However, the Committee noted that the RAPID-axSpA study included some people with non-radiographic axial spondyloarthritis who had switched to a second or third TNF-alpha inhibitor. The Committee heard from the company that the study showed that, after 2 years, the clinical response was the same for those receiving a second-line TNF-alpha inhibitor as those receiving a first-line TNF-alpha inhibitor. The Committee also heard that the study showed the disease was more likely to respond to a second treatment in people whose first treatment had failed because of adverse events, intolerance or lost efficacy than in people whose disease did not respond to initial treatment. The Committee concluded that predicting response to a second agent was difficult because it may or may not be affected by the reason for switching. The clinical experts agreed that the relative efficacy of a second TNF-alpha inhibitor would be comparable in non-radiographic spondyloarthritis and ankylosing spondylitis. The Committee

concluded that sequential treatment with TNF-alpha inhibitors is likely to be beneficial, but that clinical data are limited.

Cost effectiveness

4.60 The Committee considered the evidence for the cost effectiveness of TNF-alpha inhibitors in ankylosing spondylitis and non-radiographic axial spondyloarthritis. It noted that although the models from the companies and the Assessment Group all used changes in BASDAI and BASFI scores to model costs and utilities, the underlying assumptions in each model were very different. The Committee noted that the Assessment Group divided the models into 3 key stages: the probability of initial response, the size of initial response for patients whose disease had responded or not, and the long-term trajectory of BASDAI and BASFI scores (conditional on response status). The Committee noted the Assessment Group's criticism that some of the company models combined the latter 2 stages. The Committee decided to focus on the Assessment Group's model for decision-making purposes.

4.61 The Committee explored the uncertainties relating to key assumptions in the Assessment Group's cost-effectiveness analysis. The Committee discussed the first key stage of the model: the probability of initial response (defined as a 50% improvement in BASDAI score). The Committee heard that in the Assessment Group's model, 'responders' had lower baseline BASDAI and BASFI scores compared with 'non-responders' (a difference that was reduced in scenario 2). The Committee noted that this assumption implied that people with more severe disease did not benefit as much from TNF-alpha inhibitors as people with less severe disease, because someone with more severe disease (higher baseline scores) must have larger absolute improvements than someone with less severe disease to achieve a BASDAI 50 response. It concluded, based on discussion with clinical and patient experts, that there was no evidence to suggest that people with severe disease were less likely to have a clinically meaningful benefit than those with less severe disease.

4.62 The Committee discussed the long-term effect of TNF-alpha inhibitors on disease progression (assessed using BASFI) in people whose disease responds to treatment. The Committee heard that most company submissions assumed

that TNF-alpha inhibitors completely prevent long term disease progression (measured by BASFI). In addition, some company submissions presented more optimistic scenarios in which physical function continued to improve beyond the initial response period, implying further improvement beyond 12 weeks, which subsequently plateaued. The Committee noted that the assumption of no deterioration (measured by BASFI) during treatment was based on small, single-arm follow-up trials that were subject to selection bias and were therefore unreliable. It heard from clinical experts that their impression was that physical function (measured by BASFI) continues to deteriorate during treatment with a TNF-alpha inhibitor, but that treatment slows the rate of deterioration. The clinical experts disagreed with the Assessment Group's assumption that a TNF-alpha inhibitor's effect on progression is delayed until year 4, and the Committee agreed that it was not clinically plausible for disease progression to slow at a specific time point during treatment. The Committee concluded that the precise effect of TNF-alpha inhibitors on the long term BASFI trajectory was uncertain. It agreed that it was biologically plausible for physical function (measured by BASFI) to continue deteriorating during TNF-alpha-inhibitor treatment, but at a slower rate compared with the natural history of the disease.

4.63 The Committee considered what happens when a patient stops TNF-alpha-inhibitor treatment. For the impact of stopping treatment on BASFI scores, the Committee noted that two rebound scenarios had been presented by the companies and the Assessment Group. In the rebound to baseline scenario, the BASFI score returns to the patient's baseline score. The alternative scenario (rebound to natural history) assumes a greater deterioration in physical function (measured by BASFI) after treatment stops, to the level that it would have been if the disease had not initially responded to therapy. The Committee heard from the clinical experts that in clinical practice patients would be most likely to rebound back to their baseline scores, rather than deteriorate to a poorer state of health than they were at baseline. The Committee concluded that the rebound to baseline scenario was the more plausible assumption of the two.

4.64 The Committee noted that the ICERs produced by the Assessment Group's base-case model for ankylosing spondylitis appeared to be consistent with the results of the company models, despite differences in the assumptions used. The Committee also noted that the ICERs for certolizumab pegol and golimumab included the discount agreed in the patient access schemes. The Committee

noted that the ICERs for adalimumab, certolizumab pegol, etanercept and golimumab compared with conventional care ranged from about £19,200 per QALY gained for certolizumab pegol (with the patient access scheme) to £21,600 per QALY gained for etanercept in the Assessment Group's base case (assuming rebound to baseline). The Committee considered that these ICERs were all within the range considered to be a cost-effective use of NHS resources and concluded that adalimumab, certolizumab pegol, etanercept and golimumab could be recommended as options for treating adults with ankylosing spondylitis whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

4.65 The Committee noted that the Assessment Group's base case ICERs for infliximab for ankylosing spondylitis (rebound to baseline scenario) were about £40,600 and £36,800 per QALY gained compared with conventional care, using the original and biosimilar list prices respectively. The Committee considered that these ICERs are above the range normally considered cost-effective in the NHS. However, the Committee noted comments received in response to the appraisal consultation document about the infusion cost of infliximab and the lower prices of the biosimilar versions of infliximab as a result of the tendering process. The Committee first discussed the infusion cost, stating that the infusion cost of infliximab was too high in the Assessment Group's model and that a recent NICE consultation document for rheumatoid arthritis had used the price of £154 for infliximab infusion. The Committee noted that the cost of infusion for infliximab used in the Assessment Group's model was £291 and was based on the Healthcare Resource Group codes for delivery of subsequent elements of chemotherapy, derived from the NHS reference costs 2012 to 2013. The Committee also noted that a range of sources had been used in other appraisals including inpatient and outpatient day costs. The clinical experts stated that infusion costs in their respective hospital trusts ranged between £140 and £168. The Committee was aware that the national tariff to deliver simple parenteral chemotherapy was £159, and the clinical experts agreed that this cost was reasonable. The Committee concluded that the cost of infliximab infusion was likely to be lower than that used in the Assessment Group's model and that the national tariff cost for delivering simple parenteral chemotherapy provided a better estimate.

4.66 The Committee considered the costs of infliximab treatment. The Committee was aware that the amount of infliximab given is based on a patient's weight and,

because infliximab is provided in 100 mg vials, there is an issue of waste. The Committee heard from the clinical experts that, in practice, infliximab vial sharing is done to avoid waste. However, the Committee agreed that it could not factor vial sharing into the analyses because there would be variation in this practice in the NHS. The Committee also heard from 1 biosimilar company that its product can be supplied in a pre-prepared bag, so that hospitals pay per milligram of drug rather than per vial. However, the Committee was unsure about what additional costs this would involve. The clinical experts stated that, although not within its marketing authorisation, the dose of infliximab is often reduced to 3 mg/kg and the time between treatments is extended. The Committee concluded that it should base its decision on analyses using the assumption that whole vials are used.

4.67 The Committee also discussed the new ICERs, presented in response to the appraisal consultation document, by the companies that market biosimilar versions of infliximab. These used lower prices to reflect the tendering process that was taking place during the consultation period. The companies' representatives present at the meeting were able to confirm that the tendering process was complete and that Commercial Medicines Unit contract prices are now available in the NHS. The Committee noted the updated base-case analyses provided by the Assessment group (that included the highest price the NHS would need to pay for infliximab based on the contract prices, and infusion costs based on the national tariff to deliver simple parenteral chemotherapy) and it agreed that these analyses showed that the cost-effectiveness of infliximab was within the range considered to be a cost-effective use of NHS resources. The Committee noted section 5.5.2 of NICE's guide to the methods of technology appraisal (2013) which states: 'When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS.' The Committee therefore concluded that infliximab could be recommended as an option for treating adults with ankylosing spondylitis whose disease has responded inadequately to, or who cannot tolerate, NSAIDs provided that the infliximab product with the lowest acquisition cost is used. People already receiving infliximab should be able to continue on their existing product.

4.68 The Committee considered the cost-effectiveness results for the TNF-alpha

inhibitors in non-radiographic axial spondyloarthritis. It noted that the ICERs produced by the Assessment Group's model, and one of the company models, were higher than the corresponding ICERs for ankylosing spondylitis. The Committee noted that the Assessment Group's base case for the rebound to baseline scenario included ICERs ranging from about £28,200 for certolizumab pegol (including the patient access scheme) to £29,800 for etanercept per QALY gained, compared with conventional care. The Committee referred to the clinical discussions, where it had concluded that the benefit of TNF-alpha inhibitors was potentially underestimated in the clinical trials because of heterogeneous patient characteristics. It also noted that the Assessment Group's assumption of a slower disease progression rate (measured by BASFI) in this condition compared with ankylosing spondylitis was not confirmed by the clinical experts, and that this would in part have driven the higher ICERs compared with ankylosing spondylitis. Taking this into account, the Committee considered that the most plausible ICERs were likely to be below those presented by the Assessment Group and agreed that the ICERs for adalimumab, certolizumab pegol and etanercept were within the range that would be considered a cost-effective use of NHS resources. The Committee concluded that adalimumab, certolizumab pegol and etanercept could be recommended as options for treating adults with non-radiographic axial spondyloarthritis whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

4.69 The Committee noted that the Assessment Group was unable to use the 2-point BASDAI change in the definition of response in their model (because of lack of data) and therefore used only BASDAI 50 to define response. The Committee noted the earlier discussions about what is used to define response in clinical practice. The Committee heard that clinical experts considered it unreasonable to restrict the definition of adequate response in clinical practice to a 50% improvement in BASDAI, because this means that someone with more severe disease (a higher baseline BASDAI score) must have a greater absolute improvement in BASDAI than someone with less severe disease to qualify for continued treatment. The Committee noted that the clinical experts had stated that a 2 unit improvement in BASDAI represents a significant and clinically meaningful change. Therefore, the Committee concluded that the decision to continue treatment in clinical practice should be based on the broader definition of response to treatment outlined in British Society of Rheumatology (BSR) guidelines and the previous technology appraisal: a reduction of the BASDAI to

50% of the baseline value, or a reduction of 2 units or more, together with a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more. If an adequate response is not achieved 12 weeks after treatment initiation, treatment should be stopped.

4.70 The Committee discussed whether it was appropriate to consider treatment with a second or third TNF-alpha inhibitor for a person whose disease does not respond to treatment or stops responding, or who has an adverse reaction or becomes intolerant to treatment. The Committee noted that results from registries in ankylosing spondylitis showed around a 30% reduction in response rate with each subsequent TNF-alpha inhibitor (10% absolute reduction). It heard from the Assessment Group that this implies that the ICER would be correspondingly higher, but that the Assessment Group had not modelled sequential use. The Committee noted that one company had explored a population containing both people receiving their first TNF-alpha inhibitor and a few switching to a subsequent TNF-alpha inhibitor. Taking into account the small number of patients switching (about 6% in their model) and the reduced efficacy of subsequent TNF-alpha inhibitors in previous treatment failures, there was only an estimated £1,000 increase in the ICER per QALY gained in the population containing both patient groups compared with the group containing only patients receiving their first TNF-alpha inhibitor. The Committee noted that the Assessment Group did not consider this analysis valid. However, the Committee considered that it was reasonable to quote an ICER for the whole population if only a small number of people switched treatments. The Committee noted earlier comments (see section 4.54) that some patients would remain on a sub-optimal treatment if they were unable to switch, at a comparable cost but with decreased QALYs. It also noted the consultation comments that other trials, including the ATTRA registry, NOR-DMARD registry, RAPID-axSpA study and RHAPSODY study, provided further data, although limited, on the efficacy of subsequent TNF-alpha inhibitor treatment. The Committee agreed that all patients receiving TNF-alpha inhibitors for ankylosing spondylitis should be recruited into the ongoing British Society for Rheumatology Ankylosing Spondylitis Register. The Committee concluded that, although there was limited cost-effectiveness evidence for subsequent TNF-alpha-inhibitor use, and an exact ICER could not be determined, it considered the ICER would be within the range considered to be cost-effective use of NHS resources and subsequent TNF-alpha-inhibitor treatment could be recommended.

4.71 The Committee was aware that, in principle, potential differences between the TNF-alpha inhibitors in their effects on extra-articular manifestations may have cost implications, but noted that there was insufficient evidence to incorporate extra-articular manifestations into the cost-effectiveness analysis. However, the Committee concluded that because the TNF-alpha inhibitors had been considered as a class, the choice of treatment for both conditions should be based on clinical appropriateness, which may include consideration of associated conditions. If different TNF-alpha inhibitors are equally suitable, the product with the lowest acquisition and administration costs should be used.

4.72 The Committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant for its consideration of the cost effectiveness of any of the technologies in this appraisal.

4.73 The Committee considered whether its recommendations were associated with any potential issues related to equality. It concluded that when using BASDAI and spinal pain VAS scores to confirm the presence of sustained active spinal disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires and make any adjustments they consider appropriate.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 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 adalimumab, certolizumab pegol, etanercept, golimumab or infliximab is the right treatment (or a patient has non-radiographic axial spondyloarthritis and the healthcare professional responsible for their care thinks that adalimumab, certolizumab pegol or etanercept is the right treatment), it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, guideline representatives and NICE project team

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 4 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)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

Professor Aileen Clarke
Professor of Public Health and Health Services Research, University of Warwick

Dr Andrew England
Senior Lecturer, Directorate of Radiography, University of Salford

Dr Ian Lewin
Honorary Consultant Physician and Endocrinologist, North Devon District Hospital

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray
Professor of Medical Cardiology, University of Glasgow

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

Dr Mohit Misra
GP, Queen Elizabeth Hospital, London

Ms Sarah Parry
Clinical Nurse Specialist – Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees
Lay Member

Ms Ellen Rule
Director of Transformation and Service Redesign, Gloucestershire Clinical Commissioning Group

Mr Stephen Sharp
Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Peter Sims
GP, Devon

Mr David Thomson
Lay member

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

Professor Olivia Wu
Professor of Health Technology Assessment, University of Glasgow

Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's guideline related to this topic, were invited to attend the first ACD meeting to observe and to contribute as advisers to the Committee.

Dr Jon Packham
Consultant Rheumatologist

Dr Louise Warburton
GP with a Special Interest in Rheumatology

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Caroline Hall and Sophie Laurenson
Technical Leads

Joanna Richardson
Technical Adviser

Bijal Joshi
Project Manager

7 Sources of evidence considered by the Committee

The assessment report for this appraisal was prepared by CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York:

- Corbett M, Soares M, Jhuti G, et al. TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233, December 2014

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Companies, professional or expert and patient or carer groups, and other consultees, were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

Companies:

- AbbVie (adalimumab)
- Merck, Sharp & Dohme (golimumab, infliximab)
- Pfizer (etanercept)
- UCB Pharma (certolizumab pegol)
- Celltrion Healthcare/Napp Pharmaceuticals (infliximab biosimilar) – (requested to be involved during assessment report consultation)
- Hospira UK (infliximab biosimilar) – (requested to be involved during appraisal consultation document consultation)

Professional or expert and patient or carer groups:

- British Society for Rheumatology

- National Ankylosing Spondylitis Society
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health
- NHS England
- Welsh government

Commentator organisations (without the right of appeal):

- Department of Health and Social Services and Public Safety, Northern Ireland (DHSSPSNI)
- Healthcare Improvement Scotland
- National Institute for Health Research Technology Assessment Programme (NETSCC)
- NHS Centre for Reviews & Dissemination and Centre for Health Economics –York
- Spondyloarthritis Guideline Development Group

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on TNF-alpha inhibitors by attending Committee discussion and/or providing a written statement to the Committee. They were also invited to comment on the ACD.

- Dr Karl Gaffney, Consultant Rheumatologist, nominated by organisation representing British Society for Rheumatology – clinical expert
- Dr Raj Sengupta, Consultant Rheumatologist, nominated by organisation representing British Society for Rheumatology – clinical expert

- Mrs Debbie Cook, Chief Executive of National Ankylosing Spondylitis Society, nominated by organisation representing National Ankylosing Spondylitis Society – patient expert
- Mr Roger Stevens, nominated by organisation representing National Ankylosing Spondylitis Society – patient expert

Representatives from the following companies attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- AbbVie (adalimumab)
- Celltrion Healthcare/Napp Pharmaceuticals (infliximab biosimilar)
- Hospira UK (infliximab biosimilar)
- Merck, Sharp & Dohme (golimumab, infliximab)
- Pfizer (etanercept)
- UCB Pharma (certolizumab pegol)

8 Update information

December 2025: We have made minor editorial changes to the wording in section 1.1 to align with the NICE guideline on spondyloarthritis in over 16s: diagnosis and management. This does not affect the meaning or intent of the guidance.

February 2016: Sections 4.41 and 4.42 have been updated with the incremental cost-effectiveness ratios (ICERs) including the patient access scheme.

ISBN: 978-1-4731-1655-9