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Adalimumab, etanercept and infliximab for ankylosing spondylitis

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Adalimumab, etanercept and infliximab for ankylosing spondylitis

Ordering information

You can download the following documents from www.nice.org.uk/TA143

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for people with ankylosing spondylitis and their carers ('Understanding NICE guidance').
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1570 (quick reference guide)
- N1571 ('Understanding NICE guidance').

This guidance is written in the following context

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

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National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
London WC1V 6NA

www.nice.org.uk

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Contents

1	Guidance	1
2	Clinical need and practice	3
3	The technologies	6
4	Evidence and interpretation	9
5	Implementation	36
6	Recommendations for further research	37
7	Related NICE guidance	38
8	Review of guidance	38
	Appendix A: Appraisal Committee members and NICE project team	39
	Appendix B: Sources of evidence considered by the Committee	44
	Appendix C: Modified New York criteria for diagnosis of ankylosing spondylitis	47

1 Guidance

1.1 Adalimumab or etanercept are recommended as treatment options for adults with severe active ankylosing spondylitis only if all of the following criteria are fulfilled.

- The patient's disease satisfies the modified New York criteria for diagnosis of ankylosing spondylitis.
- There is confirmation of sustained active spinal disease, demonstrated by:
 - a score of at least 4 units on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) **and**
 - at least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (VAS).

These should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment.

- Conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated or recommended dosage for 4 weeks has failed to control symptoms.

1.2 When using BASDAI and spinal pain VAS scores to inform conclusions about whether or not sustained active spinal disease is present, healthcare professionals should be mindful of the need to secure equality of access to treatment for patients with disabilities and patients from different ethnic groups. There are circumstances in which it may not be appropriate for healthcare professionals to use a patient's BASDAI and spinal pain VAS scores to inform their conclusion about the presence of sustained active spinal disease. These are:

- where the BASDAI or spinal pain VAS score is not a clinically appropriate tool to inform a clinician's conclusion on the presence of sustained active spinal disease because of a patient's learning or other

disabilities (for example, sensory impairments) or linguistic or other communication difficulties

or

- where it is not possible to administer the BASDAI or spinal pain VAS questionnaire in a language in which the patient is sufficiently fluent for it to be an appropriate tool to inform a conclusion on the presence of sustained active spinal disease, or there are similarly exceptional reasons why use of a patient's BASDAI or spinal pain VAS score would be an inappropriate tool to inform a conclusion on the presence of sustained active spinal disease in that individual patient's case.

In such cases, healthcare professionals should make use of another appropriate method of assessment, which may include adapting the use of the questionnaire to suit the patient's circumstances.

The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with sections 1.3 and 1.4.

- 1.3 It is recommended that the response to adalimumab or etanercept treatment should be assessed 12 weeks after treatment is initiated, and that treatment should be only continued in the presence of an adequate response as defined in section 1.4.
- 1.4 For the purposes of this guidance, an adequate response to treatment is defined as a:
 - reduction of the BASDAI score to 50% of the pre-treatment value or by 2 or more units **and**
 - reduction of the spinal pain VAS by 2 cm or more.
- 1.5 Patients who have experienced an adequate response to adalimumab or etanercept treatment, as defined in section 1.4, should have their condition monitored at 12-week intervals. If the response to treatment, as defined in section 1.4, is not maintained, a repeat assessment should be made after a

further 6 weeks. If at this 6-week assessment the response defined in section 1.4 has not been maintained, treatment should be discontinued.

- 1.6 For patients who have been shown to be intolerant of adalimumab or etanercept before the end of the 12-week initial assessment period, as in section 1.3, the other one of this pair of TNF- α inhibitor treatments is recommended as an alternative treatment.
- 1.7 Prescription of an alternative TNF- α inhibitor is not recommended in patients who have either not achieved an adequate initial response to treatment with adalimumab or etanercept, as defined in section 1.4, or who experience loss of the initially adequate response during treatment.
- 1.8 It is recommended that the use of adalimumab or etanercept for severe active ankylosing spondylitis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of this condition.
- 1.9 Infliximab is not recommended for the treatment of ankylosing spondylitis.
- 1.10 Patients currently receiving infliximab for the treatment of ankylosing spondylitis should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

- 2.1 Ankylosing spondylitis is an inflammatory disease of unknown cause. It is one of a group of conditions known as the seronegative spondyloarthropathies. The principal feature of ankylosing spondylitis is inflammation of the sacroiliac joint at the base of the spine (sacroiliitis) followed by inflammation rising along the spine. The result is back pain and stiffness. Inflammation at entheses (the sites where ligaments and tendons attach to bone) can lead to new bone development and joint fixation (ankylosis). The large peripheral joints (hips, shoulders and knees) may also be involved, and the eyes and cardiovascular system can also be affected.

Systemic involvement may be significant. Disease damage is progressive and irreversible and there is increased risk of spinal fracture later in life.

- 2.2 Although symptoms can occur at any stage of life, onset of ankylosing spondylitis is typically in the late teenage years and twenties. The diagnosis of ankylosing spondylitis may not be made until many years after the onset of symptoms. The modified New York criteria for a diagnosis of ankylosing spondylitis are set out in the British Society for Rheumatology (BSR) guidelines (2004) for prescribing TNF- α blockers in adults with ankylosing spondylitis (see appendix C). Ankylosing spondylitis is nearly three times as common in men as it is in women, and men are also more likely to develop severe spinal disease.
- 2.3 The course of ankylosing spondylitis is variable, but the majority of patients have continuous disease activity with fluctuations in symptom severity known as 'flares' against the background of persistent symptoms. The disease can be severe, causing spinal fusion, pronounced incapacity and significant deformities. There is a need for joint replacement surgery in some patients. About a third of people with ankylosing spondylitis may be unable to work altogether, with a further 15% reporting some changes to their working lives. In addition, ankylosing spondylitis is associated with an increased risk of death: it is estimated that patients have a standardised mortality ratio of 1.5 or greater. According to BSR guidelines, the excess mortality is mainly accounted for by cardiac valvular disease, amyloidosis and fractures.
- 2.4 The prevalence of ankylosing spondylitis is unknown, although it has been estimated to range from 0.05% to 0.23% (based on data from the UK and Hungary). The Assessment Group considered that data from a Finnish study provide more accurate estimates of the prevalence and incidence of ankylosing spondylitis for a UK population. In that study, the prevalence of 'clinically significant ankylosing spondylitis' was estimated to be 0.15%. The annual incidence was calculated to be 6.9 per 100,000. Using mid-2004

population figures for England and Wales, this suggests that there are approximately 2300 new cases each year.

- 2.5 There are three key elements to ankylosing spondylitis that are assessed in clinical trials: disease activity, physical function and structural damage. A number of assessment tools have been developed to measure these. For example, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most commonly used instrument to measure the inflammatory activity of ankylosing spondylitis. The BASDAI is a validated, composite index that records patients' responses to six questions relating to the five major symptoms of ankylosing spondylitis: fatigue, axial pain, peripheral pain, stiffness and enthesopathy. Responses are recorded on 10 cm visual analogue scales (VAS).
- 2.6 Physical function is widely assessed through the use of the Bath Ankylosing Spondylitis Functional Index (BASFI). The BASFI is a patient-assessed, validated, composite index made up of 10 questions that address function and the patient's ability to manage their ankylosing spondylitis. As with the BASDAI, responses are recorded on a 10 cm VAS.
- 2.7 Structural damage and disease progression are primarily evaluated using radiography. Two instruments used to assess structural damage are the Bath Ankylosing Spondylitis Radiology Index (BASRI) and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).
- 2.8 The Assessment in Ankylosing Spondylitis (ASAS) working group has developed a set of response criteria commonly used in ankylosing spondylitis clinical trials. The ASAS criteria relate to improvement across a set of four domains including physical function (as measured using the BASFI) and 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 greater than 20% and an absolute change of 10 or more points on the 0–10 cm VAS in at least three of the four domains. In the fourth domain there must be no worsening by a similar amount. Other

definitions of ASAS response (ASAS 50 and ASAS 70), based on improvements of 50% and 70%, respectively, are also used to measure outcomes in clinical studies.

- 2.9 Therapies aim to provide symptom relief and improve spinal mobility. Conventional therapy for ankylosing spondylitis includes non-drug interventions (for example, physiotherapy) and drug treatment. The drugs used include non-steroidal anti-inflammatory drugs (NSAIDs) and other drugs, for example, sulfasalazine and methotrexate, that are classed as disease-modifying agents when used in rheumatoid arthritis. Physiotherapy, exercise and NSAIDs are often first-line therapies. It has been reported that the benefits of sulfasalazine and methotrexate in ankylosing spondylitis are variable and that these disease-modifying anti-rheumatic drugs (DMARDs) may be more beneficial in treating peripheral joint involvement, but not with spinal symptoms.
- 2.10 There is no clear evidence that NSAIDs alter the structural progression of the disease. This, and the side-effect profile of these drugs, has led clinicians to use NSAIDs for symptomatic control rather than as continuous therapy in the majority of patients.

3 The technologies

Adalimumab

- 3.1 Adalimumab (Humira, Abbott Laboratories Ltd) is a human-sequence antibody that binds specifically to tumour necrosis factor alpha (TNF- α) and neutralises its biological function by blocking its interaction with cell-surface TNF- α receptors. TNF- α is a cytokine that mediates inflammation and modulates the cellular immune response. Adalimumab has UK marketing authorisation for the treatment of severe active ankylosing spondylitis in adults who have had an inadequate response to conventional therapy.

- 3.2 According to the summary of product characteristics (SPC), common adverse events reported during adalimumab therapy include injection-site reactions and infections. Uncommon adverse events included non-serious allergic reactions. Before treatment begins all patients must be evaluated for both active and inactive (latent) tuberculosis infection. Adalimumab is contraindicated in patients with moderate to severe heart failure, active tuberculosis or other active infections. The SPC specifies a number of uncommon but serious adverse events that may be related to the immunomodulatory activity. For full details of side effects and contraindications, see the SPC.
- 3.3 Adalimumab is administered every 2 weeks via subcutaneous injection. The SPC states that a clinical response is usually achieved within 12 weeks of treatment and that 'continued therapy should be carefully reconsidered in a patient not responding within this time period'. The net price for a 40-mg prefilled syringe or pen is £357.50 (excluding VAT; British national formulary [BNF], edition 53). The annual cost of adalimumab for 26 doses at a dose of 40 mg every 2 weeks is £9295. Costs may vary in different settings because of negotiated procurement discounts.

Etanercept

- 3.4 Etanercept (Enbrel, Wyeth Pharmaceuticals) is a recombinant human TNF receptor fusion protein that inhibits the activity of TNF- α . Etanercept is licensed for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.
- 3.5 The most frequent adverse events reported during etanercept therapy include injection-site reactions, infections and in some instances allergic reactions. The SPC states that etanercept is contraindicated in people with sepsis or risk of sepsis, active infections like tuberculosis, and hypersensitivity to the active substance or excipients. The SPC specifies a number of uncommon but serious adverse events that may be related to the

immunomodulatory activity. For full details of side effects and contraindications, see the SPC.

- 3.6 Etanercept is administered by subcutaneous injection either twice a week or once a week depending on the dose. The net price for a 25-mg vial is £89.38 and the net price of a 50-mg vial is £178.75 (excluding VAT; BNF edition 53). The annual cost of etanercept using either 52 once-weekly doses or 104 twice-weekly doses is £9295. Costs may vary in different settings because of negotiated procurement discounts.

Infliximab

- 3.7 Infliximab (Remicade, Schering-Plough Ltd) is a chimeric monoclonal antibody that binds with high affinity to TNF- α and neutralises its activity. Infliximab is licensed for the treatment of ankylosing spondylitis in patients who have severe axial symptoms and elevated serological markers of inflammatory activity, and whose ankylosing spondylitis has responded inadequately to conventional therapy.
- 3.8 The most common adverse events reported during infliximab therapy include acute infusion-related reactions, infections, delayed hypersensitivity reactions and in some instances allergic reactions. The SPC states that infliximab is contraindicated in people with moderate or severe heart failure, active tuberculosis and, before treatment is initiated, people must be screened for both active and inactive tuberculosis. The SPC also specifies a number of uncommon but serious adverse events related to the immunomodulatory activity. For full details of side effects and contraindications, see the SPC.
- 3.9 Infliximab is administered by intravenous infusion over 2 hours at weeks 0, 2 and 6, and thereafter every 6–8 weeks. The SPC states that if there is no response by 6 weeks (that is, after two doses), no additional treatment with infliximab should be given. The net price for a 100-mg vial is £419.62 (excluding VAT; BNF edition 53). For a 75-kg adult, each dose of 5 mg/kg

requires four 100-mg vials at a cost of £1678. The three loading doses cost £5034 in total, with an approximate annual cost following the loading doses of between £15,100 and £11,700 depending on whether infusions are repeated every 6 or 8 weeks. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (see appendix B).

4.1 *Clinical effectiveness*

The Assessment Group found nine randomised controlled trials (RCTs) that met the inclusion criteria for their review. All these studies were placebo controlled and all participants continued with some form of standard treatment such as NSAIDs with or without DMARDs.

Adalimumab

- 4.1.1 There were two RCTs comparing adalimumab with placebo. In the larger of the two studies (ATLAS), 315 patients were randomised to adalimumab or placebo. In the smaller study (Canadian), 82 patients were randomised to adalimumab or placebo. The entry criteria for both studies specified that participants must have active ankylosing spondylitis that had responded inadequately to one or more NSAIDs. People in whom one or more DMARDs had failed were also included.
- 4.1.2 Both studies were double blind in design and, in both, adalimumab was given at a dose of 40 mg by subcutaneous injection every 2 weeks. Treatment was for 24 weeks, after which both active and placebo groups were switched to open-label treatment with adalimumab. The primary endpoint was the proportion of ASAS 20 responders at week 12. Those who had not reached an ASAS 20 response on assessment at weeks 12, 16 or 20 were offered the option of 'early-escape' open-label

treatment with adalimumab. Participants who chose this option were counted only as 'non-responders' in the analysis of primary and secondary endpoints. This has implications when comparing the results of these studies with previous studies of TNF- α inhibitors. Earlier studies did not include this 'early-escape' option and therefore would include those who responded later than 12 weeks in their analyses of outcomes. For this reason the Assessment Group did not include 24-week data for adalimumab in their meta-analysis.

- 4.1.3 In the ATLAS study the primary endpoint (ASAS 20 at week 12) was reached by 58.2% of the adalimumab group and 20.6% of the placebo group ($p < 0.001$). In the Canadian ankylosing spondylitis study, the respective corresponding ASAS 20 response rates were 47.2% and 21.5%. The difference did not reach conventional levels of statistical significance in the smaller study ($p = 0.06$). Meta-analysis results showed that the pooled relative risk of an ASAS 20 response was 2.43 (95% confidence interval [CI], 1.76 to 3.35). The corresponding relative risks for ASAS 50 and ASAS 70 responses were 3.22 (95% CI, 1.98 to 5.23) and 5.47 (95% CI, 2.43 to 12.31), respectively.
- 4.1.4 The mean reduction in BASDAI score at 12 weeks in the ATLAS study was 2.55 (based on 0–10 cm VAS) in the adalimumab group compared with 0.86 in the placebo group ($p < 0.001$).
- 4.1.5 The adjusted BASFI score at 12 weeks in the ATLAS study was reduced by a mean of 1.72 (scale of 0–10) in the adalimumab group compared with 0.55 (8.0% reduction from baseline) in the placebo group ($p < 0.001$).
- 4.1.6 The manufacturer's submission reports that potential biomarkers of synovitis (matrix metalloproteinase-3) and type II collagen degradation (urinary type II collagen C-telopeptide) were significantly suppressed by adalimumab in the Canadian ankylosing spondylitis study. This may

suggest inhibition of structural damage. The manufacturer concludes that further research is required to demonstrate the relationship of these markers with structural damage.

Etanercept

- 4.1.7 There were five studies of etanercept versus placebo included in the Assessment Group review. The studies compared etanercept, at a dose of 25 mg administered twice a week, with placebo. One of the studies also had a third arm in which etanercept was given at a dose of 50 mg once a week. All the studies were double blind, and ASAS 20 response at 12 weeks was the stated primary endpoint with the exception of one study where the primary endpoint was 50% improvement in disease activity using BASDAI scores. The duration of the studies varied from 6 weeks to 24 weeks.
- 4.1.8 Meta-analysis results showed that the pooled relative risk of an ASAS 20 response was 2.13 at 12 weeks (95% CI, 1.73 to 2.63) and 2.53 at 24 weeks (95% CI, 1.80 to 3.57). The corresponding relative risks for ASAS 50 and ASAS 70 responses at 12 weeks were 3.53 (95% CI, 2.50 to 4.98) and 3.38 (95% CI, 2.10 to 5.45), respectively, and at 24 weeks the relative risks for ASAS 50 and ASAS 70 responses were 3.96 (95% CI, 2.37 to 6.63) and 4.59 (95% CI, 2.32 to 9.07), respectively.
- 4.1.9 Four of the five etanercept studies reported BASDAI scores. According to meta-analysis based on the three studies that reported BASDAI score at 12 weeks, the additional reduction in BASDAI score (on a scale of 0–10) achieved with etanercept versus placebo (weighted mean difference) was 1.67 (95% CI, 1.24 to 2.10). At 24 weeks the additional reduction was 2.0 (95% CI, 1.39 to 2.61), based on the study by Davis and colleagues only.
- 4.1.10 The Assessment Group meta-analysis found an additional lowering in BASFI score of 1.48 (95% CI, 1.13 to 1.83) with etanercept compared

with placebo at 12 weeks and 1.42 (95% CI, 0.95 to 1.89) at 24 weeks (on a scale of 0–10).

4.1.11 Radiographic outcome data are only available from observational follow-up. Patients in one study were eligible to enter a 2-year open-label follow-up study to provide longer-term data including radiographic outcomes. X-rays taken at baseline in the double-blind study were compared with films at week 48 of the extension or at early termination. The mean changes in mSASSS over this period of time for the cervical, lumbar and overall spine images were 0.1, -0.1 and 0.1, respectively. There were no changes in median mSASSS scores.

Infliximab

4.1.12 The Assessment Group included two randomised, placebo-controlled studies of infliximab in their review. In the larger of the two studies, (ASSERT), participants were randomised to placebo or infliximab infusion at a dose of 5 mg/kg at weeks 0, 2, 6 and every 6 weeks thereafter. The primary endpoint was the proportion of ASAS 20 responders at week 24. The smaller study included 70 patients randomised to placebo or infliximab. The dose of infliximab was 5 mg/kg at weeks 0, 2 and 6, and the primary endpoint was the proportion of patients achieving a 50% reduction in BASDAI at 12 weeks. In both studies the inclusion criteria specified that patients had to have a BASDAI score of 4 or greater (scale of 0–10) and a spinal pain score of 4 or greater measured on a 10 cm VAS.

4.1.13 In the ASSERT study the primary endpoint (ASAS 20 at week 24) was reached by 61.2% of the infliximab group and 19.2% of the placebo group ($p < 0.001$). Meta-analysis showed that the pooled relative risk of an ASAS 20 response with infliximab versus placebo was 4.11 at 12 weeks (95% CI, 2.62 to 6.44). At 24 weeks the relative risk of an ASAS 20 response was 3.18 (95% CI, 1.99 to 5.08), based on ASSERT only.

- 4.1.14 The mean reduction in BASDAI score (0–10) at 12 weeks in the ASSERT study was 2.9 in the infliximab group versus 0.4 in the placebo group. The corresponding figures from the smaller study were 3.2 and 0.6. In the Assessment Group meta-analysis, the additional reduction in BASDAI score achieved with infliximab versus placebo (weighted mean difference) was 2.46 at 12 weeks (95% CI, 1.97 to 2.95).
- 4.1.15 The mean additional reduction in BASFI score (0–10) at 12 weeks in the ASSERT study was 1.7 (confidence interval is confidential information) in the infliximab group compared with the placebo group.
- 4.1.16 The manufacturer's submission refers to one study that showed less radiographic progression in people treated with infliximab for 2 years than in people receiving conventional treatment. The change in mSASSS was not statistically significant. Findings on magnetic resonance imaging from the ASSERT study showed a 72.9% reduction in spinal inflammation score (using a specially developed scoring system) observed at 24 weeks in the infliximab group versus no change in the placebo group.

Pooled results

- 4.1.17 The Assessment Group also assessed the TNF- α inhibitors as a class versus placebo. ASAS 20 data indicated a significant advantage of TNF- α inhibitor therapy over placebo at 12 weeks and 24 weeks (relative risk 2.52; 95% CI, 2.14 to 2.98, and relative risk 2.80; 95% CI, 2.11 to 3.71, respectively). At 12 weeks, the results of meta-analysis showed an additional mean reduction in BASDAI score of 1.89 (95% CI, 1.55 to 2.23), and an additional mean reduction in BASFI score of 1.46 (95% CI, 1.24 to 1.69). The Assessment Group also undertook a longitudinal meta-analysis based on correlation data between two time points which produced results that were nearly identical to the standard meta-analysis.

Indirect comparison

4.1.18 The Assessment Group did indirect comparisons of the TNF- α inhibitors. No statistically significant differences were found in ASAS response rates. For BASDAI, although there was a greater mean reduction in its score for infliximab treatment than for adalimumab and etanercept treatment at 12 weeks, this difference was no longer statistically significant at 24 weeks. In both cases the comparison favoured infliximab, but the differences were marginal. For infliximab and etanercept, a 24-week comparison was also possible, and this found that the difference in BASDAI was no longer statistically significant. For BASFI there was a significant difference between infliximab and adalimumab at 12 weeks and between infliximab and etanercept at 24 weeks.

Adverse events

4.1.19 There were few serious adverse events reported in the clinical studies. For the drugs given subcutaneously (that is, adalimumab and etanercept), injection-site reactions were the most commonly reported adverse events.

4.2 *Cost effectiveness*

Published economic evaluations

4.2.1 In their literature search, the Assessment Group identified six full economic evaluations that met the inclusion criteria. Only one study compared TNF- α inhibitors with each other (etanercept with infliximab). None of the economic evaluations considered adalimumab. Only one of the studies was UK-based and that study compared infliximab with placebo. Three of the studies extended beyond 1 year using observational data. The cost-effectiveness results were difficult to compare because of the varying approaches adopted and limited information available from the abstracts.

4.2.2 The Assessment Group also reviewed studies that examined the cost impact of ankylosing spondylitis. The Assessment Group found that the majority of the total costs of ankylosing spondylitis were indirect (that is, costs due to lost work productivity).

Submitted economic evaluations

4.2.3 All three manufacturers provided economic evaluations. All evaluations adopted an NHS perspective, although Abbott (adalimumab) and Schering-Plough (infliximab) also considered costs from a societal perspective. Costs and benefits in all cases were discounted at 3.5%. None of the models attempted to make any direct or indirect comparisons between the TNF- α inhibitors.

Adalimumab – manufacturer’s model

4.2.4 The manufacturer’s economic evaluation – structured as a patient-based transition-state model – compared the use of adalimumab plus NSAIDs versus treatment with NSAIDs alone. This model incorporated patient-level data from the Canadian ankylosing spondylitis and ATLAS RCTs, and aimed to simulate treatment decisions based on the BSR guidelines. The trial populations included patients who would not have met BSR eligibility criteria; for example, patients who were intolerant of, or whose ankylosing spondylitis had responded inadequately to, fewer than two NSAIDs.

4.2.5 The model consisted of two components. The first used short-term trial data (first 48 weeks) as noted above. The second component simulated long-term outcomes for responders for up to 30 years.

4.2.6 In the short-term component of the model, response to treatment was defined as a reduction of BASDAI to 50% of the pre-treatment value or a fall of 2 units or more, plus a reduction of the spinal pain VAS score (over the last week) by 2 cm or more. From week 48 onwards, the BASDAI and spinal pain VAS scores of each patient (including those on

standard therapy) were assumed to remain stable. In contrast, BASFI scores of patients on standard therapy were assumed to increase by 0.05 units per year. For adalimumab-treated patients, BASDAI and BASFI scores remained stable as long as the patient remained on adalimumab therapy. A separate scenario analysis was conducted to assess the impact of assuming no effect of adalimumab on BASFI progression.

- 4.2.7 After 48 weeks it was assumed that patients would discontinue adalimumab treatment at a rate of 10% per year. When patients on adalimumab discontinued therapy, it was assumed that their BASDAI and BASFI scores would return to the average values of the patients in the model who were managed by conventional therapy. In the economic evaluation the rebound occurred rapidly (that is, within the next measurement period).
- 4.2.8 Disease-specific costs were based on ordinary least squares (OLS) regression of BASDAI and BASFI data from OASIS (the Outcome in Ankylosing Spondylitis International Study). Only BASDAI measurements were used to predict costs in the base-case analysis. In a secondary analysis, BASFI scores only were used to estimate costs. Costs of managing adverse events were included in the model.
- 4.2.9 In the base-case analysis, BASDAI and BASFI scores were used jointly to estimate health-related quality of life. A mapping exercise was undertaken, which used health-utility index scores collected in the Canadian ankylosing spondylitis and ATLAS studies.
- 4.2.10 In the base-case, the incremental cost-effectiveness ratio (ICER) over a 30-year time horizon was about £23,000 per QALY gained. Univariate sensitivity analyses on a number of parameters including annual discontinuation rates were undertaken; ICERs varied from £18,000 per QALY gained to around £27,000 per QALY gained (over 30 years).

Etanercept – manufacturer’s model

- 4.2.11 The manufacturer’s model compared the use of etanercept plus NSAIDs with NSAIDs alone. The model generated a hypothetical patient population based on patient-level data from two RCTs and an open-label extension. The principal RCT evidence used in the model was drawn from a single study (n = 356). The time horizon was up to 25 years.
- 4.2.12 Response to treatment was determined by BSR criteria, and was evaluated at 12 and 24 weeks within the model. Response rates in the placebo arms of the trials were used to model outcomes for the comparator in the economic evaluation. Responders obtained an initial health gain in BASDAI/BASFI scores. Patients were assumed to remain at the new BASDAI/BASFI levels for the duration of their response to treatment.
- 4.2.13 It was assumed in the base-case that responders to etanercept did not progress in terms of BASDAI and BASFI scores while on treatment, and that the rate of disease progression in non-responders was 0.3 units per year for both BASDAI and BASFI. In terms of the rate of withdrawal from etanercept treatment, it was assumed that initial responders to treatment would discontinue etanercept at a rate of 10% per year. In the model, patients who withdrew from etanercept would continue to receive NSAIDs, and it was therefore assumed that disease progression would mirror that of the comparator arm.
- 4.2.14 Assumptions were made concerning the impact of withdrawal from treatment on BASDAI and BASFI scores. In the base-case, BASDAI and BASFI scores returned to baseline levels (base-case). In an alternative scenario, the disability of a person was assumed to have progressed while on treatment. On withdrawal from etanercept, scores returned to a state worse than baseline.

- 4.2.15 Changes in BASDAI and BASFI scores drive changes in both predicted disease costs and utility. Regression analyses of EQ-5D (n = 356) and SF-36 (n = 511) data collected from ankylosing spondylitis patients were used to establish a relationship between changes in BASDAI and BASFI and utility. In the base-case analysis, the output from the EQ-5D regression was used to estimate quality-adjusted life years (QALYs).
- 4.2.16 Disease-related costs were based on a retrospective analysis of resource use by 147 ankylosing spondylitis patients attending the Staffordshire Rheumatology Centre. Adverse events were not considered in the modelling because the trials did not report statistically significant differences in adverse events between the two arms.
- 4.2.17 In the base-case, the ICER was reported to be around £13,200 over a 25-year time horizon. A number of univariate sensitivity analyses were undertaken. When a utility model based on SF-36 data was used, ICERs were found to vary between £17,000 and £70,000 per QALY gained. Probabilistic sensitivity analysis indicated that over a 25-year time period, etanercept has an 88% probability of being cost effective at a threshold willingness to pay of £15,000.

Infliximab – manufacturer’s model

- 4.2.18 The manufacturer’s model is based on a combined decision tree and Markov chain structure, and compares infliximab versus ‘standard therapy’. Two analyses were described, one based on the 24-week outcomes of the ASSERT trial and the other on a smaller study of up to 12 weeks. The placebo groups in these studies were assumed to have received standard therapy as these studies allowed the concomitant use of NSAIDs.
- 4.2.19 In the base-case, infliximab dosing was modelled as per the administration schedule in the clinical trials; that is, 5 mg/kg every 6 weeks, with an additional infusion after 2 weeks. The SPC allows

dosing to take place every 6–8 weeks. The drug dose was calculated based on the mean body weights reported in the two included studies.

4.2.20 Patient-level data from the two RCTs informed the decision-tree component of the model. At 12 or 24 weeks (depending on the randomised period of the trial), continuation on infliximab treatment was determined by BSR criteria relating to BASDAI response at 12 weeks. (In the case of the ASSERT data, 24-week data were used.) All patients then entered the Markov model, which has three health states (on-treatment, off-treatment and dead) and an annual cycle.

4.2.21 The age at the start of the economic evaluation was fixed at 40 years and the analysis adopted a time horizon of 70 years. In addition, it was assumed that neither ankylosing spondylitis nor its treatments would affect mortality. Costs and utilities were assigned based on regression models controlling for BASDAI, BASFI, age and gender, and bootstrapping for the probabilistic analysis.

4.2.22 It was assumed that infliximab non-responders and placebo patients would have a natural disease progression of 0.07 BASFI units per year (however, in the submitted model this was not implemented for infliximab patients who withdrew from treatment). In terms of withdrawal rate from treatment with infliximab, the analysis assumed an annual drop-out rate of 15%. Patients who withdrew from infliximab treatment were assigned the BASFI and BASDAI scores of the no-treatment group, reduced by the underlying natural progression of BASFI during the years of treatment. In other words, the rebounded BASFI score remains lower than for those patients in the comparator arm.

4.2.23 In the base-case, the reported ICERs in the original submission were under £20,000. However, this was based on an inaccurate model, which in part allowed patients who withdrew from infliximab treatment to avoid being assigned an 'off-treatment' disease progression. On correcting this error, the manufacturer reported base-case 70-year ICERs of

approximately £27,000 to £28,000 per QALY gained (depending on which of the two studies is used to inform the calculation). In contrast, the Assessment Group found that, on correcting the model within an Excel replica, the lifetime ICERs were between £41,000 and £50,000 per QALY gained. The manufacturer also reported corrected ICERs for the scenario in which disease progression while on treatment is assumed to be 50% of natural history (that is, 0.035 units per year), and the ICERs rise to between £34,000 and £35,000 per QALY gained.

4.2.24 The manufacturer of infliximab also provided estimates from its model with assumptions that it stated were identical to those set out in the analysis described in sections 4.2.35 to 4.2.40. These estimates are detailed in section 4.2.40.

The Assessment Group model

4.2.25 The Assessment Group examined the use of adalimumab, etanercept and infliximab compared with 'conventional treatment'. 'Conventional treatment' was defined in terms of the placebo arms of two adalimumab RCTs. The group explored the cost effectiveness of these interventions over the short term (1 year) and over a time horizon of up to 20 years.

4.2.26 The Assessment Group assumed that all three interventions were of equal effectiveness. Short-term effectiveness was modelled using response rates (based on BSR criteria) from the pooled week-12 data from the adalimumab and etanercept trials, and week-24 response rates after pro rata imputation of the missing data from the Wyeth study. The 12-week response rate for infliximab was slightly lower than those reported for the other drugs, so adopting the pooled estimates for all three drugs did not disadvantage infliximab.

4.2.27 Under base-case assumptions, from week 30 onwards it was assumed that spontaneous recovery without treatment would occur at a rate of 17.1% as identified in the patient-level analysis of two adalimumab RCTs

supplied in the Abbott submission. This assumption was explored in univariate and multivariate sensitivity analyses. In univariate sensitivity analyses, in which it was assumed there was no spontaneous recovery in the placebo arm, the ICERs for adalimumab and etanercept over a 20-year time horizon decreased from £92,000 (base-case) to £57,000. The ICER for infliximab decreased from £168,000 (base-case) to £109,000.

- 4.2.28 The Assessment Group model assumed that patients withdraw from TNF- α inhibitor treatment at a rate of 15% per year, although in sensitivity analyses, rates of 7% and 24% were also explored. The annual withdrawal rate (after the first 12 months) was applied to the difference in response rate between the two arms of the evaluation, rather than the absolute number of responders.
- 4.2.29 The Assessment Group model took into account the cost of adverse events. Disease-related costs were estimated by fitting an exponential cost model to the weighted aggregate OASIS data. BASFI was used as the major predictor of costs because it was considered to reflect long-term disease progression.
- 4.2.30 Health-related quality of life was estimated using the utility model provided by Schering-Plough on the grounds that it used a comparatively larger sample of UK ankylosing spondylitis patients, and also because it incorporated age and gender variables.
- 4.2.31 The Assessment Group adopted a long-term increase in BASFI scores of 0.07 units per year for the conventional treatment comparator arm of the model. This progression rate is applied for all periods after week 20 in the model.
- 4.2.32 Over a 1-year time horizon, base-case ICERs for adalimumab and etanercept were essentially the same (around £55,000). In contrast, the ICER for infliximab was over £124,000.

4.2.33 With respect to modelling beyond 12 months, the results for adalimumab were considered as representative of etanercept, and only the former were provided. In contrast with the manufacturers' models, ICERs increase steadily from year 2 onwards.

4.2.34 Univariate and multivariate sensitivity analyses were undertaken. Multivariate sensitivity analyses identified scenarios in which adalimumab/etanercept could be considered cost effective, with ICERs ranging from £12,000 to £118,000. Important factors influencing the long-term cost effectiveness of these two drugs included assumptions about spontaneous recovery, withdrawal rate from treatment and the BASFI progression rate. Multivariate sensitivity analyses on the infliximab results identified no scenario in which the ICER dropped below £35,000.

Further analysis by the Decision Support Unit

4.2.35 Following consultation on the submissions from the three manufacturers and the Assessment Group, the Committee requested additional analysis to be carried out by the Decision Support Unit (DSU) to identify reasons for the large differences in the cost-effectiveness results and to determine whether the differences in the results still existed when an agreed set of common parameter values were included.

4.2.36 The DSU included the following common parameter values in all three manufacturers' models and in the Assessment Group's model: 0% spontaneous response rate without TNF- α inhibitor treatment; BASFI progression rate 0.07 per year without TNF- α inhibitor treatment; rate of withdrawal from TNF- α inhibitors 7% per year; baseline BASDAI/BASFI averages: 6.5/5.6; Assessment Group base-case assumptions for utility (which were the same as in the Schering-Plough utility model); and Assessment Group base-case assumptions for cost parameters.

4.2.37 The DSU found that using a common set of parameter values in the manufacturers' models gave relatively consistent results for each of the drugs. The two cost-effectiveness models based on different trials submitted by Schering Plough gave ICERs over 20 years of £27,000 or £24,000 for adalimumab/etanercept and £58,000 or £50,000 for infliximab. The Wyeth model gave ICERs of £20,000 for etanercept and £39,000 for infliximab. The Abbott model gave results of £17,000 for adalimumab and £43,000 for infliximab (over a 30-year time horizon). In comparison, after applying the same parameter values to the Assessment Group's model, the DSU found very different ICERs: £42,000 for adalimumab/etanercept and £82,000 for infliximab. The DSU concluded that the differences in the manufacturers' and Assessment Group's models could not be explained by the set of parameter values examined in all the models.

4.2.38 By carrying out a reconciliation, the DSU found that a key driver of the differences between the Assessment Group's model and those of the manufacturers was the assumption made about the extent to which responders to TNF- α inhibitor treatment experience disease progression (that is, show BASDAI and BASFI progression). The Assessment Group model implicitly assumes that responders to TNF- α inhibitor treatment will experience disease progression. This results from fitting a quadratic equation to short-term clinical trial data, and extrapolating this over the exploratory 20-year time horizon. In the manufacturers' models it is assumed there will be no disease progression. The DSU remarked that there is little evidence on how the course of disease progression in ankylosing spondylitis is altered following TNF- α inhibitor treatment.

4.2.39 The DSU applied the assumption of no disease progression after 1 year for TNF- α inhibitor treatment responders to the Assessment Group's model that included the common parameter values. This gave revised results for adalimumab/etanercept of £30,000 per QALY gained, down

from £42,000 per QALY gained. If no disease progression was assumed for adalimumab or etanercept after 20 weeks, the ICER becomes £22,000 per QALY gained. The equivalent ICER for infliximab if no disease progression was assumed after 20 weeks was £49,000 per QALY gained. The DSU commented that the assumption of zero response in the placebo arm was a favourable one. If this assumption is not made, the ICERs for the Assessment Group's model move from £30,000 per QALY gained to £47,000 per QALY gained if no disease progression is assumed after the first year, and from £22,000 per QALY gained to £31,000 per QALY gained, if no disease progression is assumed after the first 20 weeks.

4.2.40 The manufacturer of infliximab provided estimates from its own model with assumptions stated to be identical to those set out in the DSU analysis. The resulting ICERs were £48,000 per QALY gained when maintenance infusions are given every 6 weeks, and £37,000 when maintenance infusions are given every 8 weeks. The manufacturer stated that infliximab tends to be dosed at the less frequent 8-week intervals in current UK practice and that therefore it is more appropriate for cost-effectiveness estimates to be based on 8-week rather than 6-week cycles. The manufacturer also provided estimates of ICERs across a range of patient weight categories. The analysis estimated that 15% of patients in the lowest weight category would require only 3 vials of infliximab per infusion, and if maintenance infusions are assumed to be given every 8 weeks, the cost per QALY gained would be £26,200 for this group of patients. The ICER for infusions every 8 weeks for this group of patients (if flat BASDAI and BASFI profiles are assumed) from week 20 onwards was £28,000 per QALY gained if it was assumed there was no response in the placebo arm, and £39,000 per QALY gained if this response was assumed to occur in 17% of patients as in the LRiG base-case. The equivalent figures with 6-week injections were £39,000 per QALY gained and £54,000 per QALY gained. The ICERs presented

by the manufacturer on the same basis as the £26,200 above, assuming 4 vials are needed (estimated to be necessary for 45% of patients in the middle weight category) would be £37,000 and for 5 vials (estimated to be necessary for 40% of patients in the highest weight category) would be £47,900 per QALY gained. The manufacturer also suggested that these estimates of cost effectiveness of infliximab would be lower due to vial optimisation (sharing vials to avoid wastage) and because in current clinical practice it is common to use a lower dose of 3 mg/kg, rather than 5 mg/kg which is recommended in the marketing authorisation.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of adalimumab, etanercept and infliximab for ankylosing spondylitis, having considered evidence on the nature of the condition and the value placed on the benefits of these drugs by people with ankylosing spondylitis, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee discussed the evidence of clinical effectiveness of TNF- α inhibitors. It noted that statistically significant improvements in measures of disease activity, functional disability and composite outcomes had been observed at 12 weeks and in some studies at 24 weeks. The Committee heard from patient experts that some people with ankylosing spondylitis who have received TNF- α inhibitors have experienced dramatic improvements both in their symptoms and in their functional ability. The Committee noted that in many studies people continued to receive NSAIDs and DMARDs alongside the study medication. The Committee understood that any effect due to concurrent therapy with NSAIDs or DMARDs during the trials was likely to be similar in both treatment arms. The Committee concluded that there is clear evidence for the clinical effectiveness of TNF- α inhibitors in people with

severe active ankylosing spondylitis compared with placebo in the short term.

- 4.3.3 The Committee discussed the long-term use of TNF- α inhibitors in the treatment of ankylosing spondylitis. The Committee was mindful that life-long use of TNF- α inhibitors in the treatment of ankylosing spondylitis may not be appropriate because of the potential for adverse events, including hypersensitivity reactions, lymphoma, worsening of heart failure and increased risk of infections such as tuberculosis. The Committee understood from clinical specialists that physicians and patients carefully evaluate the potential risks and benefits when considering whether to start TNF- α inhibitor therapy and whether to continue treatment in the longer term.
- 4.3.4 The Committee was aware that the TNF- α inhibitors could potentially affect long-term outcomes related to structural damage within the spine and the effects of ankylosis, but that this was an area of uncertainty and RCT evidence for this effect is currently lacking. The Committee heard from clinical specialists that these agents were likely to be of similar clinical effectiveness in the treatment of spinal disease.
- 4.3.5 The Committee considered the differences in clinical effectiveness between adalimumab, etanercept and infliximab from the results reported in the principal RCTs. It noted that no head-to-head trials had been identified, and discussed the indirect comparisons undertaken by the Assessment Group. The Committee noted from the indirect comparisons that no statistically significant differences were found in the primary outcome, ASAS responses rates. It noted that infliximab treatment was associated with a greater mean reduction in BASDAI score than adalimumab and etanercept treatment at 12 weeks, but that this difference was no longer statistically significant at 24 weeks. The Committee concluded that it would not be appropriate to infer a

difference in the clinical effectiveness of the drugs using the results generated from these indirect comparisons.

- 4.3.6 The Committee considered the potential for the TNF- α inhibitors to differ in their effectiveness in treating features of ankylosing spondylitis other than spinal disease; for example, peripheral arthritis and extra-articular manifestations such as inflammatory bowel disease and uveitis. The Committee was aware that, in principle, potential differences between the TNF- α inhibitors in their effects on these additional features would be important to people with ankylosing spondylitis, but noted that differences between TNF- α inhibitors had not been demonstrated in the evidence base. The Committee noted that most of the evidence on the benefits of TNF- α inhibitors in treating the extra-articular manifestations was based on a population of people with specific conditions, such as psoriasis, inflammatory bowel disease or uveitis. The Committee noted that the pivotal studies in people with ankylosing spondylitis did not evaluate the effectiveness of these drugs in treating extra-articular manifestations of the disease. In addition, the relevant ankylosing spondylitis evidence presented for infliximab and adalimumab was based on observational studies or follow-up studies, most of which were of small sample size and were not designed to determine the effectiveness of these drugs on extra-articular manifestations. Therefore, the Committee concluded that there was no compelling evidence on which it could reliably distinguish between the clinical effectiveness of TNF- α inhibitors on these bases in either the short term or the long term.
- 4.3.7 The Committee considered the evidence for the cost effectiveness of TNF- α inhibitors. The Committee discussed the varying structures, assumptions and input data in each of the manufacturers' economic models and in the Assessment Group model. In particular, it discussed the uncertainties relating to the assumptions that had to be made in

order to estimate ICERs over the long time horizons appropriate for this chronic disease. These uncertainties relate to:

- the long-term effectiveness of TNF- α inhibitors in controlling disease activity
- whether TNF- α inhibitors slow or halt the progression of structural damage in the spine and functional disability related to ankylosis
- the proportion of people with ankylosing spondylitis who may experience a significant improvement in their condition without TNF- α inhibitor treatment
- the rate at which the disease progresses in those who respond to treatment, those who do not respond and those on placebo
- the rate at which people are expected to withdraw from TNF- α inhibitor treatment
- the degree to which a person's condition might be expected to rebound if therapy is withdrawn
- the time horizon appropriate for considering the cost effectiveness of TNF- α inhibitor treatment of ankylosing spondylitis.

4.3.8 In addition to the issues listed in section 4.3.7, the Committee noted further issues for consideration. The assumption of long-term continuous treatment made in the models did not correspond to the view that it may be advisable to stop TNF- α inhibitor treatment after a period of time given the uncertainties around the risks and benefits of long-term therapy. The Committee understood that physicians and patients carefully evaluate the potential risks and benefits when considering the long-term continuation of TNF- α inhibitor treatment. The Committee also discussed issues raised, about the manufacturers' models, in the assessment report and the corresponding responses provided by the manufacturers during consultation. The Committee discussed the reconciliation exercise and additional analysis carried out by the DSU, and agreed that the key assumptions influencing the estimates of cost

effectiveness of all models were those concerning the long-term progression of BASDAI and BASFI while people are receiving treatment, and those concerning improvements in the disease in people in the placebo arm. It considered the remaining common assumptions that had been used to reconcile the models (as detailed in section 4.2.36) to be plausible except for the assumption of no spontaneous resolution of symptoms, equivalent to absence of a placebo response (as discussed in section 4.3.10).

4.3.9 The Committee discussed the worsening of disease activity and functional ability while people are receiving TNF- α inhibitor treatment. It understood that in current clinical practice, which is set out in the BSR 2004 guidelines, TNF- α inhibitor treatment is discontinued in people who do not have a clearly established and sustained response to treatment. Furthermore, the Committee considered it biologically plausible that functional deterioration might be prevented in those people in whom the inflammatory process is controlled, as indicated by a sustained reduction in disease activity. As such, it would be reasonable to model stable BASDAI and BASFI profiles in the long term if use of TNF- α inhibitor treatment is continued only in people who maintain a sustained response to treatment as per the BSR guidelines. The Committee considered the DSU's assumption of stable BASDAI and BASFI after 20 weeks to be appropriate in this context. The resulting ICER of £22,000 per QALY gained calculated by the DSU for adalimumab and etanercept using the Assessment Group model, in which BASDAI and BASFI remain stable after 20 weeks, was also considered to be plausible in this context. The Committee noted that the ICER for infliximab, using the stable BASDAI and BASFI profiles, was £49,000 per QALY gained.

4.3.10 The Committee considered that the assumption around no spontaneous resolution of symptoms, equivalent to absence of a placebo response, was unlikely. It heard from the DSU that if a 17% response in the

placebo arm was assumed (as in the original Assessment Group model) then the ICER of £22,000 per QALY gained would increase to £31,000 per QALY gained for etanercept and adalimumab. The Committee considered that these two figures represented a reasonable range of cost effectiveness based on the evidence. The equivalent figures for infliximab were £49,000 to £65,000 per QALY gained. Therefore, on balance, taking into account all of its previous assumptions, the Committee concluded that adalimumab and etanercept for the treatment of severe ankylosing spondylitis could be considered a cost-effective use of NHS resources in the context of achieving a continued response to treatment.

4.3.11 The Committee discussed the cost effectiveness of infliximab in further detail. The Committee agreed with the assumption in the Assessment Group model of equivalent clinical effectiveness for the three drugs as this was consistent with the Committee's considerations set out in sections 4.3.4 and 4.3.5. The Committee therefore concluded that higher resource use and costs associated with infliximab accounted for its reduced cost effectiveness compared with adalimumab and etanercept.

4.3.12 The Committee then considered the information provided by the manufacturer about factors that could reduce the estimated ICERs of infliximab compared with placebo. This information included alternative assumptions for: the frequency of maintenance infusions (8-week rather than 6-week intervals), vial optimisation, varying patient weight categories and the use of a reduced dose of 3 mg/kg rather than 5 mg/kg. It noted that the manufacturer had reported a base-case ICER of £48,000 per QALY gained from its own model, with assumptions stated to be identical to the DSU analysis.

4.3.13 The Committee discussed the frequency of maintenance infusions and noted that the manufacturer had presented ICERs based on infusions every 8 weeks and not every 6 weeks. The Committee was aware that

the marketing authorisation indicated a 6- or 8-week dosing schedule but noted that the pivotal trials for infliximab used a 6-week maintenance dose and that there was no RCT evidence to support the assumption of equal clinical effectiveness if the less frequent 8-week dosing schedule was assumed as a routine. The Committee therefore did not accept the ICER of £37,000 per QALY gained owing to the lack of RCT evidence for the effectiveness of the 8-week schedule; moreover, it did not consider the 8-week schedule to be appropriate as the primary basis for the ICER.

4.3.14 The Committee also discussed the cost effectiveness of infliximab for people in different weight categories presented by the manufacturer. The Committee noted that for people in the lowest weight group (between 40 and 60 kg), for whom only 3 vials per infusion would be required, the manufacturer had reported an ICER of £26,000 per QALY gained assuming 8-week infusion intervals. The Committee considered that the equivalent ICER from the Assessment Group model was between £28,000 and £39,000 per QALY gained. However, it considered that these ICERs were underestimates because they were based on 8-week maintenance infusions while assuming the same efficacy as 6-week infusions derived from the pivotal RCTs. The Committee thought that the most plausible range of ICERs for this weight category, using injections every 6 weeks, was between £39,000 and £54,000 per QALY gained (based on the assumptions underlying the ICERs in section 4.3.10).

4.3.15 The Committee then discussed the ICERs presented by the manufacturer, assuming vial optimisation, of £20,800, £31,600 and £42,500, based on the average weights in three weight groups of 50 kg, 70 kg and 90 kg. It also noted that the equivalent ICER from the Assessment Group model based on an average weight of 50 kg and maintenance infusions every 6 weeks was £33,000. The Committee therefore thought that the ICERs presented by the manufacturer were underestimates, noting that these were calculated assuming maintenance infusions every 8 weeks rather than 6 weeks. It discussed

the mean and distribution of the weights of people with ankylosing spondylitis, noting that fewer than 15% of people had been estimated, based on the BSR biologics registry, to weigh less than 60 kg. The Committee thought that the assumption of 3.74 vials on average per person for the whole group (as assumed in the Assessment Group and DSU base-case calculations), based on the distribution of body weight in the BSR biologics registry, was reasonable. Thus the Committee was not persuaded that the assumptions presented by the manufacturer around vial sharing are representative of what would occur in routine practice in the population of people with ankylosing spondylitis.

4.3.16 The Committee also discussed the suggestion that the infliximab dose used in clinical practice is often 3 mg/kg rather than the 5 mg/kg dose indicated in the marketing authorisation. The Committee fully appreciated that using the lower dose would also lower the acquisition cost of infliximab but was not persuaded that the ICERs provided, based on the 3 mg/kg dose, were valid because of the lack of RCT evidence to support the assumption of equivalence in clinical effectiveness between the lower dose and that specifically indicated in the marketing authorisation. In addition, the assumption of routine use of 8-week maintenance infusions was not considered appropriate in view of the considerations discussed in section 4.3.13.

4.3.17 The Committee discussed patient preferences for particular drugs, which may be influenced by the route and the frequency of their administration. It heard from patient experts that people value having a choice of therapy. The Committee considered the Institute's principles on social value judgements in this regard; in particular, the principle to consider individual choice and respect for autonomy, but not with the effect of promoting the use of interventions that are not cost effective. Because two cost-effective treatment options (etanercept and adalimumab) are recommended for the treatment of ankylosing spondylitis, and because the available evidence persuaded the Committee that infliximab was not

cost effective in treating this condition, it concluded that it could not recommend the use of infliximab simply on the basis of another treatment choice.

4.3.18 The Committee further discussed the circumstances of the use of infliximab for those people who have difficulties with self-injecting. It took into account the results reported in sections 4.2.39 and 4.2.40, indicating that etanercept and adalimumab had substantially lower ICERs of £22,000 to £31,000 per QALY gained compared with infliximab (£49,000 to £65,000 per QALY gained). The Committee considered the difference in cost effectiveness between infliximab and etanercept or adalimumab. The Committee noted that treatment with a choice of either etanercept or adalimumab would provide people with ankylosing spondylitis with alternative dosing schedules (once or twice weekly and once fortnightly, respectively). The Committee furthermore considered that the subcutaneous dosing schedules of etanercept or adalimumab were such that alternative approaches could readily be identified for people who had difficulties with self-injection, including assistance in the home (for example, from family members or healthcare personnel in the home) or visits to a healthcare centre for their injections. The Committee noted that if people with ankylosing spondylitis were assumed to require assistance from a healthcare professional (for example, their General Practitioner) for their injections instead of self-injecting, the cost effectiveness of adalimumab and etanercept would worsen owing to the additional costs of administration. However, the Committee concluded that on balance these additional costs of administration would not on average outweigh the higher costs of infliximab treatment to the extent that infliximab would be more cost effective than adalimumab or etanercept in this patient group. The Committee discussed whether certain groups of people could be disadvantaged by this approach. The Committee concluded that people who have difficulties with self-injecting would not be disadvantaged in the use of anti-TNF- α treatment because

a choice of two treatments with differing dosing schedules for subcutaneous injection would be available and that alternative approaches for those unable to self-inject could readily be made available. The Committee did not identify any disadvantages resulting from the use of subcutaneous injections with assistance as compared with intravenous infusion, given that both methods require the involvement of other people to administer the treatment and that infusion can only be administered over a period of time in a medical environment.

4.3.19 The Committee discussed criteria for starting therapy with TNF- α inhibitors. It was in agreement in general with the criteria set out in the BSR guidelines for prescribing TNF- α inhibitors in adults with ankylosing spondylitis in terms of diagnostic criteria (modified New York criteria), confirmation of sustained active spinal disease, and failure of conventional treatment to control symptoms. Confirmation of sustained active spinal disease should be demonstrated by a score of at least 4 units on the BASDAI and by at least 4 cm on the 0 to 10 cm spinal pain VAS, on two occasions at least 12 weeks apart without any change of treatment. Conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated or recommended dosage for 4 weeks should have failed to control symptoms. The Committee was aware that, to ensure that chronicity of severe disease was established, and to avoid treatment of flares of disease activity that might be expected to spontaneously remit, it was essential that these criteria were strictly adhered to. The Committee further concluded that the use of adalimumab and etanercept for severe active ankylosing spondylitis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of this condition.

4.3.20 The Committee discussed the assessment and definition of adequacy of initial response following initiation of treatment with TNF- α inhibitors, and

the applicability of a stopping/continuation rule in people who do not experience an adequate initial response. The Committee concluded that the decision to continue treatment should be based upon the response to treatment assessed at 12 weeks after initiation. If the response criteria, defined as a reduction of the BASDAI to 50% of the pre-treatment value, or a reduction of 2 units or more, together with a reduction of the spinal pain VAS by 2 cm or more, had not been experienced, treatment should be discontinued.

4.3.21 The Committee discussed long-term treatment with TNF- α inhibitors. It discussed the importance of monitoring with regard to discontinuing treatment in people who were not experiencing a continued response to TNF- α inhibitor therapy. The Committee was in agreement in general with the criteria set out in the BSR guidelines for prescribing TNF- α inhibitors which include monitoring a response to treatment and when treatment should be withdrawn. It was satisfied that the BSR guidelines had been broadly reflected in the cost-effectiveness analysis. The Committee concluded that response to treatment should be monitored at regular intervals of 12 weeks. If a response of a reduction of the BASDAI to 50% of the pre-treatment value, or by 2 units or more, together with a reduction of the spinal pain VAS by 2 cm or more has not been maintained, there should be a repeat assessment after 6 weeks. If the original response has not been maintained on both occasions, treatment should be discontinued.

4.3.22 The Committee discussed whether it was appropriate to consider treatment with a second TNF- α inhibitor for a person who does not meet the required initial response to treatment (a reduction of the BASDAI to 50% of the pre-treatment value or by 2 units or more, together with a reduction of the spinal pain VAS by 2 cm or more) or experiences a loss of response later during treatment. The Committee considered that it would be inappropriate to recommend sequential treatment in the

absence of RCT evidence demonstrating that such a strategy would be clinically or cost effective. Thus the Committee concluded that if the person has not had an adequate initial response to treatment, or experiences loss of response later during treatment, treatment with an alternative TNF- α inhibitor is not recommended. It noted, however, that there may be circumstances in which a break in the treatment of a person whose ankylosing spondylitis has responded to a TNF- α inhibitor may be appropriate, for example because of a desire to become pregnant. In such circumstances, the Committee thought it would be appropriate for the same TNF- α inhibitor to be resumed after the treatment break if there had previously been an adequate maintained response.

4.3.23 The Committee also discussed the possibility of using an alternative TNF- α inhibitor for people who developed intolerance or have contraindications to either adalimumab or etanercept. It concluded that it would be appropriate to use the other one of this pair of TNF- α inhibitor treatments as an alternative treatment if this intolerance was evident before the first clinical-effectiveness assessment at 12 weeks after initiation of therapy.

4.3.24 The Committee discussed the need for a register of people receiving TNF- α inhibitors for severe active ankylosing spondylitis. It considered that such a register would be important to obtain the information needed to assess the long-term risks and benefits of treatment with TNF- α inhibitors and that consideration should be given to this in the future.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and

resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA143).
- Costing template incorporating a costing report to estimate the savings and costs associated with implementation.
 - Audit support for monitoring local practice.

6 Recommendations for further research

The Committee considered that further research into the effectiveness of TNF- α inhibitors in ankylosing spondylitis should include the following.

- 6.1 Studies to investigate the long-term effects of TNF- α inhibitors in people with ankylosing spondylitis, including their effects on disease activity, functional status, structural damage, quality of life and adverse effects.
- 6.2 Studies to establish the appropriate duration and pattern of long-term treatment with TNF- α inhibitors.

- 6.3 Studies to examine whether ankylosing spondylitis responds to more than one TNF- α inhibitor given sequentially.
- 6.4 The collection of data through a register of people with ankylosing spondylitis receiving TNF- α inhibitor treatment in England and Wales will be essential to addressing the issues described above.

7 Related NICE guidance

- Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 130 (2007). Available from: www.nice.org.uk/TA130
- Adalimumab for the treatment of psoriatic arthritis. NICE technology appraisal guidance 125 (2007). Available from: www.nice.org.uk/TA125
- Etanercept and efalizumab for the treatment of adults with psoriasis. NICE technology appraisal guidance 103 (2006). Available from: www.nice.org.uk/TA103
- Etanercept and infliximab for the treatment of adults with psoriatic arthritis. NICE technology appraisal guidance 104 (2006). Available from: www.nice.org.uk/TA104

8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 8.2 The guidance on this technology will be considered for review in October 2010.

Andrew Dillon
Chief Executive
May 2008

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its 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. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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

Radiologist, St George's Hospital, London

Professor A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Amanda Adler

Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Member

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Professor Christopher Eccleston

Director Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Ms Linda Hands

Consultant Surgeon, John Radcliffe Hospital

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, Newcastle University

Dr Catherine Jackson

Clinical Senior Lecturer in Primary Care Medicine, University of Dundee

Dr Terry John

General Practitioner, The Firs, London

Professor Richard Lilford

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

Dr Simon Maxwell

Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queen's Medical Research Institute

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne

Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson

Lay Member

Dr Stephen Saltissi

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Debbie Stephenson

Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner & Associate Professor, Department of Primary Care & General Practice, University of Birmingham

Dr Simon Thomas

Consultant Physician, General Medicine and Clinical Pharmacology, Newcastle Hospitals NHS Trust

Mr David Thomson

Lay Member

Dr Luke Twelves

General Practitioner, Cambridgeshire PCT

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Director of Commissioning, NHS East of England

B NICE project team

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

David S Chandiwana

Technical Lead

Helen Chung

Technical Adviser

Alana Miller

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG).

McLeod C, Bagust A, Boland A et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis (May 2006).

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document (ACD). Consultee organisations are provided with the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Abbott Laboratories Ltd
- Wyeth Pharmaceuticals
- Schering-Plough Ltd

II Professional/specialist and patient/carer groups:

- Arthritis and Musculoskeletal Alliance
- Arthritis Care
- Back Care
- British Brain and Spine Foundation
- British Health Professionals in Rheumatology
- British Orthopaedic Association
- British Pain Society
- British Society of Rehabilitation Medicine
- British Society for Rheumatology
- Changing Faces
- National Ankylosing Spondylitis Society

- Pain Concern
- Physiotherapy Pain Association
- Primary Care Rheumatology Society
- Royal Association for Disability and Rehabilitation
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal College of Physicians
- Royal College of Physicians of Edinburgh

III Commentator organisations (without the right of appeal):

- Arthritis Research Campaign
- British National Formulary
- Liverpool Reviews and Implementation Group, University of Liverpool
- Medicines and Healthcare Products Regulatory Agency
- National Coordinating Centre for Health Technology Assessment
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Society for Back Pain Research

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor 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 adalimumab, etanercept and infliximab for ankylosing spondylitis by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Richard Bridgeman, nominated by the National Ankylosing Spondylitis Society – patient expert
- Dr Karl Gaffney, Consultant Rheumatologist, Norfolk and Norwich University Hospital, nominated by the Royal College of Physicians – clinical specialist
- Dr Andrew Keat, Consultant Rheumatologist, Northwick Park Hospital, nominated by the British Society for Rheumatology – clinical specialist
- Fergus Rogers, nominated by the National Ankylosing Spondylitis Society – patient expert
- Professor Roger Sturrock, Professor of Rheumatology, University of Glasgow, nominated by the British Society of Rheumatology – clinical specialist
- Jane Skerret, nominated by the National Ankylosing Spondylitis Society – patient expert
- Terry Orsler, nominated by the National Ankylosing Spondylitis Society – patient expert

Appendix C: Modified New York criteria for diagnosis of ankylosing spondylitis

A definite diagnosis of ankylosing spondylitis requires the radiological criterion and at least one clinical criterion to be satisfied as defined below.

Radiological criterion

Sacroiliitis at least grade 2 bilaterally or grade 3 or 4 unilaterally.

Clinical criteria

- Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.
- Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values correlated for age and sex.

All reasonable measures should be taken to ensure that symptoms are due predominantly to ankylosing spondylitis and that alternative causes, including spinal fracture, disc disease and fibromyalgia, are excluded.