NICE National Institute for Health and Care Excellence

Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis

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Contents

1 Guidance

This guidance partially replaces 'Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 36) issued in March 2002.

For details, see 'About this guidance'.

1.1 The tumour necrosis factor alpha (TNF-α) inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics.

- Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
- Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

1.2 TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy.

1.3 Treatment with TNF-α inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS28 of 1.2 points or more.

1.4 After initial response, treatment should be monitored no less frequently than 6-monthly intervals with assessment of DAS28. Treatment should be withdrawn if an adequate response (as defined in 1.3) is not maintained.

1.5 An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.

1.6 Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended.

1.7 Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules.

1.8 Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.

1.9 Initiation of TNF-α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.

2 Clinical need and practice

2.1 Rheumatoid arthritis (RA) is a chronic and progressive disabling condition characterised by inflammation of the synovial tissue of the joints. It causes tenderness and stiffness of joints with progressive destruction of them, and other symptoms such as pain and fatigue. It affects between 0.5% and 1% of the population, or approximately 400,000 people, in England and Wales. Of these, approximately 15% have severe disease. RA affects three times as many women as men and has a peak age of onset of 40–70 years.

2.2 In RA, the synovium becomes enlarged because of an increase in the number of synovial cells (hyperplasia), infiltration by white blood cells and formation of new blood vessels. There is an increase in fluid-containing inflammatory cells in the joint cavity (effusion) and, secondary to this, thinning of the bone around the joint (periarticular osteoporosis). Erosions of the bone occur where synovial tissue meets cartilage and bone, and these, together with the periarticular bone thinning, lead to long-term irreversible damage of the structure and function of the joint.

2.3 Internationally agreed criteria (American College of Rheumatology [ACR] criteria of 1987) for the diagnosis of RA require four of the following features to be present: morning stiffness in joints exceeding 1 hour; physician-observed arthritis of three or more areas with soft tissue swelling; arthritis involving hand joints; symmetrical arthritis; rheumatoid skin nodules; a positive blood test for rheumatoid factor; and radiographic changes typical of rheumatoid disease. However, clinicians may diagnose RA without reference to these criteria and patients might not meet formal disease classification criteria early on in their disease.

2.4 The course of RA is heterogeneous and variable. However, a number of factors have been identified as being associated with poor prognosis. These include the presence of rheumatoid factor or anti-cyclic citrullinated peptide (CCP) antibodies, high erythrocyte sedimentation rate or C-reactive protein (CRP) levels, early radiographic evidence of erosions and the presence of swollen and tender joints. Within 2 years of diagnosis, patients usually experience moderate disability, and after 10 years 30% are severely disabled.

Approximately one third of patients cease work because of the disease. Life expectancy in patients with RA is also reduced. For example, a 50-year-old woman with RA is expected to die 4 years earlier than a 50-year-old woman without RA.

2.5 Conventional treatment aims to control pain and inflammation, and to reduce joint damage, disability and loss of function, thereby improving quality of life. It involves a combination of pharmacological and non-pharmacological interventions. Conventional drug therapy relies on various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and DMARDs. DMARDs act to ameliorate symptoms and slow progression of structural damage; they are used as monotherapy or in combination, often with concomitant steroids. Recent advances suggest that the goal is to treat the disease with DMARDs soon after diagnosis, and to try and achieve remission. Methotrexate and sulfasalazine are DMARDs often used as initial therapy. Non-drug therapies include surgery, physiotherapy and occupational therapy.

2.6 Several measures have been developed to assess response to treatment in RA. For example, the ACR response criteria (ACR20, 50 and 70) require a specified percentage improvement (20, 50 or 70% respectively) in tender joint count, swollen joint count, global assessments, pain, disability and circulating inflammatory markers (for example, erythrocyte sedimentation rate or CRP). The disease activity score (DAS) is an alternative scoring system developed in Europe. It is calculated using a formula that includes counts for tender and swollen joints (53 and 44 joints respectively), an evaluation of general health by the patient (on a scale of 0 to 100), and a measure of circulating inflammatory markers. DAS28 is similar to DAS above but uses only 28 joints for assessment. A DAS28 score greater than 5.1 is considered to be indicative of high disease activity, between 5.1 and 3.2 of moderate disease activity and less than 3.2 of low disease activity. A patient scoring less than 2.6 is defined as being in remission. The European League Against Rheumatism (EULAR) response criteria are based on the DAS measure. A decrease in DAS28 score of 0.6 or less is considered to show a poor response, while decreases greater than 1.2 points indicate a moderate or good response, dependent on whether an individual's DAS28 score at the end point is above or below 3.2 respectively. The Stanford Health Assessment Questionnaire (HAQ) is one

component of the ACR criteria and scores ability to perform daily activities from 0 (least disability) to 3 (most severe disability). The modified Sharp score is a measure of joint damage as assessed radiographically, and is based on joint-space narrowing and erosions.

3 The technologies

Adalimumab

3.1 Adalimumab (Humira, Abbott Laboratories) is a human-sequence antibody that binds specifically to TNF-α and neutralises its biological function by blocking its interaction with cell-surface TNF-α receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration. Adalimumab is licensed for the treatment of moderate to severe, active RA in adults when the response to DMARDs, including methotrexate, has been inadequate, and for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. The summary of product characteristics (SPC) states that adalimumab should be given in combination with methotrexate, except where methotrexate is not tolerated or is considered inappropriate.

3.2 According to the SPC, common adverse events reported during adalimumab therapy include injection-site reactions and infections. Before initiation of therapy, 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. For full details of side effects and contraindications, see the SPC.

3.3 Adalimumab is administered at a dose of 40 mg every other week via subcutaneous injection. In monotherapy, if patients experience a decrease in response the dose may be increased to 40 mg every week. The net price for a 40-mg prefilled syringe is £357.50 (excluding VAT; 'British National Formulary', edition 53 [BNF53]). The annual cost of adalimumab for 26 doses at a dose of 40 mg every other week 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-α-receptor fusion protein. It interferes with the inflammatory cascade by binding

to TNF-α, thereby blocking its interaction with cell-surface receptors. Etanercept is licensed for use in adults with active RA whose response to DMARDs, including methotrexate, has been inadequate. Etanercept is also indicated in the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. The SPC states that for patients who have had an inadequate response to conventional DMARDs, etanercept should be given in combination with methotrexate, except where methotrexate is not tolerated or is considered inappropriate.

3.5 The most frequent adverse events reported during etanercept therapy include injection-site reactions, infections and allergic reactions. The SPC specifies a number of uncommon but serious adverse events related to the immunomodulatory activity. Etanercept is contraindicated in patients with sepsis or at risk of sepsis and those with other active infections. There are no monitoring requirements. For full details of side effects and contraindications, see the SPC.

3.6 Etanercept is administered by subcutaneous injection at a dose of 25 mg twice weekly. Alternatively, the SPC allows for a dose of 50 mg once weekly. The net price for a 25-mg vial is £89.38 (excluding VAT; BNF53). 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, thereby neutralising its activity. Infliximab is licensed for the treatment of active RA where the response to DMARDs, including methotrexate, has been inadequate, and for patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. The SPC specifies that infliximab must be used in combination with methotrexate.

3.8 The most common adverse events reported during infliximab therapy include acute infusion-related reactions, infections and delayed hypersensitivity

reactions. Infliximab is contraindicated in people with moderate or severe heart failure or active infections. Before treatment is initiated, people must be screened for both active and inactive tuberculosis. The SPC lists 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 at a dose of 3 mg/kg by intravenous infusion over 2 hours at weeks 0, 2 and 6, and thereafter every 8 weeks. A change to the licensed indication for infliximab means that if there is an inadequate response or a loss of response, consideration may be given to increasing the dose of infliximab stepwise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. The net price for a 100 mg vial is £419.62 (excluding VAT; BNF53). Assuming an average weight of 70 kg and a dose of 3 mg/kg, each dose of infliximab requires three vials at a cost of £1259. The three loading doses cost £3777, with an annual cost following the loading doses of between £7553 and £8812 depending on whether 6 or 7 doses are required. 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

Twenty-nine randomised controlled trials (RCTs) were identified as meeting the criteria for inclusion in the assessment report (nine adalimumab studies, 11 etanercept studies and nine infliximab studies). However, the primary meta-analyses were based on 20 studies of varying durations (8 weeks to 2 years) that included comparisons of interventions when given at licensed dose or equivalent. Due to the timing of the appraisal, only the evidence base where infliximab was given at a dose of 3 mg/kg every 8 weeks was examined. Of the 20 studies, four recruited only patients with early RA (disease duration of 3 years or less) who were also methotrexate naive, while 16 included patients for whom conventional DMARDs had provided an inadequate effect. In these studies disease duration varied widely. This section summarises clinical effectiveness outcomes in terms of ACR20 response, ACR70 response, HAQ score, modified Sharp score, serious adverse events and malignancies where these data were collected in the studies, except where they were marked 'commercial in confidence'.

Adalimumab

4.1.1 Of nine adalimumab studies, six were included in the primary analyses based on licensed doses of 40 mg every other week or equivalent (n = 2660). One study (PREMIER) recruited methotrexate-naive patients with early RA (n = 799), and made a three-way comparison of adalimumab monotherapy, methotrexate monotherapy and adalimumab combined with methotrexate. Four studies included patients in whom conventional DMARDs had previously provided an inadequate response. Two of these studies compared adalimumab directly with placebo and two added adalimumab to existing methotrexate therapy where the ongoing response was inadequate. A final study (STAR) added adalimumab to existing anti-rheumatic therapy, and enrolled predominantly patients who had had an inadequate response to conventional DMARDs. In three of the studies the primary end point was ACR20 response. In two studies the primary end points included ACR50 response, modified total

Sharp score, and HAQ score. In one study the primary end points were safety outcomes (STAR).

4.1.2 In patients with early RA (the PREMIER study) adalimumab monotherapy was statistically significantly more effective than methotrexate for change in radiographic joint damage (modified Sharp score) at 2 years (weighted mean difference [WMD] −4.90; the confidence interval [CI] has been marked as commercial in confidence). However, at 2 years differences for ACR20 response (relative risk [RR] 0.88 [95% CI, 0.75 to 1.03]), ACR70 response (RR 0.99 [95% CI, 0.75 to 1.30]) and HAQ score (WMD 0.00 [95% CI, −0.13 to 0.13]) did not reach statistical significance. In the same study, 2-year results show that the addition of adalimumab to methotrexate led to a statistically significant improvement when compared with methotrexate alone across a number of outcomes, including ACR20 response (1.24 [95% CI, 1.08 to 1.42]), ACR70 response (1.64 [95% CI, 1.30 to 2.07]), and modified Sharp score (WMD −8.50 [the CI has been marked as commercial in confidence]), but not a statistically significant difference for HAQ score (WMD −0.10 [95% CI, −0.23 to 0.03]).

4.1.3 Data were meta-analysed from five studies that included patients for whom conventional DMARDs had previously provided an inadequate response. In these studies the durations of treatment and follow-up periods were between 12 and 52 weeks. The meta-analysis suggested that adalimumab was statistically significantly more effective than control (either placebo or existing anti-rheumatic therapy) across a range of outcomes. These included ACR20 response (RR 2.11 [95% CI, 1.84 to 2.42]), ACR70 response (RR 5.22 [95% CI, 3.45 to 7.89]), HAQ score (WMD −0.31 [95% CI, −0.36 to −0.26]) and modified Sharp score per year (WMD −2.20 [95% CI, −3.33 to −1.07]).

4.1.4 Across the five studies that included patients for whom conventional DMARDs had previously provided an inadequate response, 113 patients (10%) taking adalimumab experienced serious adverse events (data for the patients in the control groups were marked commercial in confidence), and 14 patients (1%) taking adalimumab developed malignancies as compared with two patients (0.3%) in the control group. In the study including patients who were methotrexate naive (PREMIER), 18.5 serious adverse events per 100 patient

years were reported for the patients taking adalimumab combined with methotrexate. This compares with 21.1 serious adverse events per 100 patient years in the adalimumab monotherapy group and 15.9 serious adverse events per 100 patient years in the methotrexate monotherapy group. In the PREMIER study, 10 malignancies were observed (excluding non-melanoma skin cancers): two in the combination treatment group, four in the adalimumab monotherapy arm, and four in the group who had received methotrexate monotherapy.

Etanercept

4.1.5 Of the 11 etanercept studies, one was excluded from the analyses because of very small patient numbers (three or four in each arm). The other 10 studies all included patients who received etanercept given at the licensed dose of 25 mg twice weekly or equivalent. Two studies included patients who had not previously had an inadequate response to methotrexate, allowing an active comparison with methotrexate. The TEMPO study included patients with early and established RA who had previously had an inadequate response to a conventional DMARD other than methotrexate, and made a three-way comparison of etanercept monotherapy, etanercept combined with methotrexate and methotrexate monotherapy (n = 682). The other study (ERA) included only patients with early RA, and compared etanercept monotherapy with methotrexate monotherapy (n = 424). Eight studies included patients for whom conventional DMARDs had provided an inadequate response. Three of these studies compared etanercept with placebo, while in the other five studies etanercept could be added to an ongoing treatment regimen: either unspecified DMARDs (1 study), methotrexate (3 studies) or sulfasalazine (1 study). The primary efficacy end points in the etanercept studies included ACR20 response, ACR50 response, change in number of swollen and tender joints, and change in modified Sharp score.

4.1.6 In the study that recruited solely patients with early RA (ERA), 2-year results show that etanercept monotherapy was statistically significantly more effective than methotrexate monotherapy for ACR20 response (RR 1.22 [95% CI, 1.06 to 1.40]) and for modified Sharp score per year (WMD −0.97 [95% CI, −1.65 to −0.29]). At 2 years the differences for ACR70 response (RR 1.23 [95% CI, 0.89

to 1.70] and HAQ score (WMD −0.10 [95% CI, −0.23 to 0.03]) did not reach statistical significance.

4.1.7 In a meta-analysis of data from eight studies including patients for whom the response to conventional DMARDs had previously been inadequate, etanercept was found to be statistically significantly more effective than control across efficacy outcomes, including ACR20 response (RR 3.59 [95% CI, 2.89 to 4.46]), ACR70 response (RR 9.44 [95% CI, 3.98 to 22.38]) and HAQ score (WMD −0.50 [95% CI, −0.59 to −0.42]). No data were available for modified Sharp score.

4.1.8 In the study (TEMPO) including patients for whom the response to conventional DMARDs (but not methotrexate) had previously been inadequate, etanercept monotherapy was statistically significantly more effective than methotrexate for ACR20 response (RR 1.28 [95% CI, 1.06 to 1.54]) and modified Sharp score per year (WMD −2.28 [95% CI, −4.11 to −0.45]), but not for ACR70 response (RR 1.46 [95% CI, 1.00 to 2.14]) or HAQ score (WMD −0.10 [95% CI, −0.23 to 0.03]). In the same study a comparison of etanercept combined with methotrexate with methotrexate alone showed a statistically significant difference favouring combination therapy for efficacy outcomes including ACR20 response (RR 1.49 [95% CI, 1.25 to 1.77]), ACR70 response (RR 2.53 [95% CI, 1.82 to 3.54]), HAQ score (WMD −0.40 [95% CI, −0.52 to −0.28]) and modified Sharp score per year (WMD −3.34 [95% CI, −5.12 to −1.56]).

4.1.9 In the studies including patients for whom the response to conventional DMARDs had been inadequate, a total of 37 patients (4%) experienced serious adverse events among those taking etanercept compared with 23 patients (5%) in the control groups (receiving either placebo or an inadequate methotrexate, sulfasalazine or unspecified DMARD regimen). In addition, across these studies a number of patients developed malignancies: two in the etanercept groups (0.2%) and five in the control groups (0.8%). In the TEMPO study, 44 patients (20%) receiving etanercept monotherapy experienced serious adverse events compared with 41 patients (18%) in the methotrexate monotherapy group, and 52 patients (23%) in the combination therapy group. In addition, five patients (2%) treated with etanercept alone and five (2%)

treated with etanercept plus methotrexate developed malignancies compared with two (1%) among those who received methotrexate alone. Data for malignancies are also available from the ERA study which show that in both the etanercept and methotrexate groups there were five patients (2%) who developed malignancies.

Infliximab

4.1.10 Of the nine infliximab studies, four were included in the primary analyses conducted by the Assessment Group. Inclusion was based on doses of infliximab, combined with methotrexate, given at the licensed dose of 3 mg/kg at 0, 2, and 6 weeks, and then every 8 weeks. Two studies compared infliximab combined with methotrexate with methotrexate alone in patients with early RA who were methotrexate naive (n = 661). The other two studies added infliximab to an ongoing methotrexate regimen where there was an inadequate response (n = 897). The primary end points varied in the four studies and included ACR20 response at 30 weeks and synovitis measured by magnetic resonance imaging (MRI).

4.1.11 In a meta-analysis of data from the two studies following up patients with early RA over 1 year, the addition of infliximab to methotrexate was statistically significantly more effective than methotrexate alone for a number of efficacy outcomes. These included ACR20 response (RR 1.17 [95% CI, 1.02 to 1.34]), ACR70 response (RR 1.57 [95% CI, 1.20 to 2.05]), HAQ score (WMD −0. 17 [95% CI, −0.29 to −0.06]) and modified Sharp score per year (WMD −3.28 [95% CI, −4.55 to −2.01]).

4.1.12 In a meta-analysis of the data from two studies including patients for whom an existing methotrexate regimen was inadequate, infliximab was found to be statistically significantly more effective compared with placebo across efficacy outcomes, including ACR20 response (RR 2.30 [95% CI, 1.90 to 2.78]), ACR70 response (RR 3.16 [95% CI, 1.89 to 5.27]), HAQ score (WMD −0.27 [95% CI, −0.35 to −0.19]) and modified Sharp score per year (−5.70 [95% CI, −8.58 to −2.82]).

4.1.13 In the study of early RA reporting serious adverse events (ASPIRE), 52 patients (14%) treated with infliximab combined with methotrexate experienced

serious adverse events, compared with 32 patients (11%) given methotrexate monotherapy. According to the published ATTRACT trial data, malignancies developed in five infliximab-treated patients during the trial (two were recurrences and three were new cases). Further information relating to serious adverse events and malignancies was marked commercial in confidence.

British Society of Rheumatology (BSR) Biologics Register

4.1.14 Observational follow-up data for all three drugs are available from the BSR Biologics Register. This was established in 2001 with the aim of capturing data on the safety and efficacy of the use of TNF-α inhibitors in patients with RA. Sample size calculations were based on being able to detect a doubling of the risk of lymphoma, and it was estimated that the register should aim to recruit 4000 unexposed patients and 4000 patients for each TNF-α inhibitor. Between October 2001 and 31 December 2004, the register recruited 8455 patients on TNF-α inhibitors and a control cohort of 1199 patients.

4.1.15 At 6-month follow up, 18%, 49% and 32% of patients were classified as having a good, moderate or poor EULAR response respectively, while at 18-month follow up, data show 17%, 38% and 44% of the cohort classified as having a good, moderate or poor EULAR response respectively. Data for the cohort as a whole show that HAQ score decreased from an average score of 2.1 at baseline to 1.8 at 6-month follow up. When only those patients remaining on TNF-α inhibitors were included, the change in HAQ score was greater, falling to 1.7 at 6-month follow up. HAQ scores at 18-month follow up appeared to be maintained for both the whole cohort and only those remaining on TNF-α inhibitors.

4.1.16 Data from the register show no overall increase in mortality, cancer or serious adverse events in the TNF-α inhibitor group compared with controls without exposure to TNF-α inhibitors. However, it should be noted that the control group had a higher rate of comorbidity, was on average older than the TNF-α inhibitor cohort (60 versus 56 years), and had a shorter disease duration (9.1 versus 13.7 years), less severe disease and less disability at baseline. In addition, the control cohort had been exposed previously to fewer DMARDs on average than had those receiving TNF-α inhibitors (two versus four).

4.2 Cost effectiveness

Published economic evaluations

4.2.1 The Assessment Group identified ten published economic analyses, of which six compared a TNF-α inhibitor with conventional DMARDs, and four compared multiple TNF-α inhibitors with conventional DMARDs. The results of the economic evaluations varied substantially. Direct comparisons between the different incremental cost-effectiveness ratios (ICERs) were not possible due to different model specifications, including time horizon, perspective and country of origin.

Submitted economic evaluations

4.2.2 Five economic models, including that of the Assessment Group, were submitted for the appraisal. All three manufacturers provided economic analyses to support their submissions, of which two considered the role of the TNF-α inhibitor as part of a drug sequence. In addition an independent economic model was submitted by the British Society of Rheumatology based on data from the Biologics Register. In the base case of each economic evaluation, cost and benefits were discounted at rates of 6% and 1.5% respectively.

Adalimumab – the manufacturer's model

4.2.3 The manufacturer developed two patient-based, state-transition models to assess adalimumab in combination with methotrexate compared with a sequence of conventional DMARDs. The first model was based on study data from patients for whom the response to DMARDs had been inadequate (ARMADA and Keystone trials). The base case modelled adalimumab in combination with methotrexate as a fourth-line treatment, with additional analyses examining first-, second- and third-line use. The second model was based on study data from patients with early RA who were methotrexate naive (PREMIER) and the base case modelled adalimumab combined with methotrexate as a first-line treatment, with additional analyses examining second- and third-line use. In the models the baseline profile was set to reflect patients in the adalimumab trials. The age of the hypothetical patients entering

both models was 54.7 years, reflecting the mean age of the patients in the trials. In the early RA model the baseline HAQ score was 1.1 and in the other model the baseline HAQ score was 1.6. ACR50 response data were used in the base case to determine response rates on each therapy.

4.2.4 Analyses based on data from patients who had previously had an inadequate response to conventional DMARDs suggest that adalimumab combined with methotrexate as a fourth-line therapy gives an estimated ICER of £17,860 per quality-adjusted life year (QALY) gained. One-way sensitivity analyses suggest a range of estimates of cost effectiveness between £14,132 and £23,821 per incremental QALY gained. ICERs for intervention as first-, second- and third-line were £19,095, £18,166 and £18,479 per QALY, respectively.

4.2.5 Analyses based on data from patients with early RA who are methotrexate naive suggest that adalimumab combined with methotrexate as a first- or second-line intervention gives estimates of incremental cost effectiveness of £23,017 and £17,559 per QALY gained, respectively. One-way sensitivity analyses around the estimate for first-line use suggest a range of estimates between £16,181 and £59,471 per incremental QALY gained.

Etanercept – the manufacturer's model

4.2.6 The manufacturer developed a Markov model with a 6-month cycle length to assess the cost effectiveness of etanercept combined with methotrexate for the first-, second- and third-line treatment of RA when compared with a sequence of conventional DMARDs. In the model, a simulated patient received a given treatment until DMARD switching occurred as a result of either failure of effectiveness or serious adverse events. A baseline HAQ score of 1.74 was assumed, and changes in HAQ score based on results from a clinical trial (TEMPO) were used as the measure of effectiveness.

4.2.7 The base-case results suggest that first-line therapy with the combination of etanercept and methotrexate has an ICER of £16,379 per QALY gained. Secondary analyses demonstrate that second- and third-line therapy have ICERs of £19,924 and £18,405, respectively. One-way sensitivity analyses gave estimates of incremental cost effectiveness ranging from £11,451 to

£29,132 per QALY for first-line therapy, £13,902 to £33,156 per QALY for second-line therapy and £13,971 to £27,528 per QALY for third-line therapy.

Infliximab – the manufacturer's model

4.2.8 A Markov model was developed by the manufacturer to examine the cost effectiveness of infliximab combined with methotrexate compared with methotrexate alone in three patient groups: those with active RA despite treatment with conventional DMARDS (established RA), those with early RA who were methotrexate naive and those with early RA who were both methotrexate naive and experiencing rapid progression. The health states in the model were defined by HAQ score. To estimate the long-term consequences of RA and model the natural history of RA, information was drawn from a North American database of 4258 patients with RA enrolled in private practices between 1981 and 1995 (ARAMIS). The effectiveness estimate was based on HAQ scores from the ATTRACT and ASPIRE trials.

4.2.9 In the base case, the model estimated the following ICERs: patients with established RA, £6228 per QALY; patients with early RA who were methotrexate-naive, £16,766 per QALY; patients with early RA who were methotrexate-naive and had rapid progression (as defined by disease duration of 3 years or less, persistent synovitis and a serum CRP value greater than 30 mg/litre), £13,000 per QALY.

4.2.10 A range of one-way sensitivity analyses were presented for key parameters. The estimates of cost effectiveness ranged from £4703 to £38,141, £13,272 to £41,015 and £10,004 to £50,546 for each of the above groups, respectively. The sensitivity analyses demonstrated that the model was particularly sensitive to assumptions concerning radiographic progression.

The BSR model

4.2.11 The BSR submitted a probabilistic decision analytical model using data from the BSR Biologics Register. The model evaluated the cost effectiveness of using TNF-α inhibitors as a class compared with conventional DMARDs.

4.2.12 The model was run over a lifetime and, for each modelled patient, analyses predicted the EULAR response category, the improvement in health utility over the first 6 months and the time to withdrawal. In addition to drug and administration costs, the costs of hospitalisation were also taken into account. The patient was moved through a series of six treatments before moving onto palliative therapy. Each hypothetical patient was run through two arms: one with TNF-α inhibitors and one without. For the base case, utility estimates were derived from the EQ-5D based on a mapping exercise from HAQ scores.

4.2.13 Two base-case scenarios were presented, one that modelled current UK practice as per the BSR Biologics Register and one that modelled the use of TNF-α inhibitors where there was withdrawal at 3 months unless the patient was classified as a EULAR moderate responder. In the former, base-case results estimated that the ICER for TNF-α inhibitors as a group, compared with conventional DMARDs, was about £23,900 per QALY gained. Modelling based on withdrawal at 3 months reduced the ICER marginally to around £22,400 per QALY. One-way sensitivity analyses around the former base case gave estimates of incremental cost effectiveness between £12,524 and £82,471, while estimates around the latter base case were between £12,283 and £335,680. Higher estimates were obtained when the assumptions relating to underlying disease progression were changed.

The Assessment Group model

4.2.14 The Assessment Group's model was an individual sampling model, which assessed the cost effectiveness of adding a TNF-α inhibitor to an existing treatment pathway for RA when compared with the same pathway of DMARDs (individually or combination) without a TNF-α inhibitor. The TNF-α inhibitor with or without methotrexate could be introduced singly as first-line, as third-line or as last active therapy before moving onto palliation.

4.2.15 In this model, initial age and sex distribution, as well as the starting distribution of HAQ scores, were based on the Norfolk Arthritis Register, a primary-care-based observational cohort of patients with inflammatory polyarthritis. HAQ score improvement was modelled as a multiplier of the starting HAQ score and was set to vary in the model. Data were based on estimates from published and unpublished literature, and were also used to derive quality of life scores.

Patients on TNF-α inhibitors were assumed to have underlying HAQ progression commensurate with the general population (a constant increase of HAQ score indicating worsening functional disability of 0.03 a year). Patients on palliation were assumed to have HAQ progression twice that of the general population, while those on other DMARDs had underlying HAQ progression of 0.045 a year. The model included a proportion of people stopping treatment at 24 weeks due to toxicity and inefficacy, which were related to the magnitude of the initial HAQ response. Joint replacement and associated costs were included in sensitivity analyses.

4.2.16 Estimates of incremental cost effectiveness for a TNF-α inhibitor as third-line therapy after the failure of two conventional DMARDs in comparison with a sequence of conventional DMARDs were calculated using data from patients who had had an inadequate response to conventional DMARDs ('late RA'). The estimates of incremental cost effectiveness for adalimumab, etanercept and infliximab, all in combination with methotrexate, were £64,400, £49,800 and £139,000 per QALY gained respectively. When an assumption of no HAQ progression while on TNF-α inhibitors was used, the ICERs fell to £30,200, £24,600 and £39,400 per QALY for adalimumab, etanercept and infliximab respectively (all with methotrexate).

4.2.17 As well as modelling third-line therapy using 'late RA' data. The Assessment Group modelled third-line therapy using the efficacy data from the trials where patients had early RA. The estimates of incremental cost effectiveness for adalimumab, etanercept and infliximab (all in combination with methotrexate) were £30,200, £28,500 and £30,400 per QALY respectively. When it is assumed there is no HAQ progression while on TNF-α inhibitor treatment, the estimates of incremental cost effectiveness for all three drugs fall to below £20,000 per QALY.

4.2.18 The model from the Assessment Group also estimated the cost effectiveness of using adalimumab or etanercept monotherapy after the failure of two conventional DMARDs. The estimates of incremental cost effectiveness using the 'late RA' data were £141,000 per QALY for adalimumab and £47,400 per QALY for etanercept assuming HAQ progression while on TNF-α inhibitors, and £41,500 and £24,400 per QALY respectively with no HAQ progression.

The corresponding figures using the 'early RA' data were £34,600 per QALY for adalimumab and £30,400 per QALY for etanercept assuming HAQ progression, and £21,200 and £18,700 per QALY respectively with no HAQ progression.

4.2.19 For the TNF-α inhibitors as first-line treatment for early RA, the estimated ICERs (versus the DMARD sequence described above) were higher than those for third-line use: adalimumab with methotrexate, £171,000 per QALY; etanercept with methotrexate, £78,100 per QALY; infliximab with methotrexate, £654,000 per QALY. Applying the assumption of no HAQ progression while on TNF-α inhibitors reduced the estimates of incremental cost effectiveness. For adalimumab, etanercept and infliximab as combination therapies with methotrexate the estimates of cost effectiveness were reduced to £37,600, £28,000 and £46,100 per QALY respectively.

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, having considered evidence on the nature of the condition and the value placed on the benefits of adalimumab, etanercept and infliximab by people with RA, 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 considered the evidence of clinical effectiveness of the TNF-α inhibitors. It agreed that studies demonstrated the efficacy of adalimumab, etanercept and infliximab in a range of populations with RA. The Committee noted that licensed indications for all three TNF-α inhibitors recommended prescription in combination with methotrexate where a patient had previously had an inadequate response to conventional DMARDs, although in the case of etanercept and adalimumab monotherapy could be prescribed if methotrexate was not tolerated or was not appropriate. The Committee understood that recommendations could only be made within the current licensed indications, which meant that TNF-α inhibitors should normally be prescribed in combination with methotrexate, although etanercept and adalimumab could be

used as monotherapy where methotrexate was not tolerated or was not appropriate.

4.3.3 The Committee noted that there were some differences in efficacy end points reported for the three agents in the individual RCTs, but that the populations included in the trials were not necessarily comparable. The Committee heard from clinical specialists that they did not consider there to be clinically significant differences in effectiveness between the TNF-α inhibitors in everyday practice and this view was supported by data from the BSR Biologics Register. The Committee understood there were no head-to-head trials comparing these agents and therefore concluded that there was no compelling evidence to distinguish between the TNF-α inhibitors on the basis of clinical effectiveness when making recommendations.

4.3.4 The Committee discussed the most appropriate method of assessing response to treatment with TNF-α inhibitors and when treatment should be initiated in clinical practice. The Committee was aware of guidance from EULAR for the management of early RA that identified prognostic factors suggestive of persistent and erosive disease. The Committee heard from clinical specialists that these factors were considered in clinical practice, but they expressed caution with using population studies to develop criteria for predicting the outcome in individual patients. The Committee noted that the DAS28 measure incorporates assessment of tender and swollen joints as well as biochemical measures of disease activity, which are prognostic factors of poor disease outcome, and also includes a measure of the patient's perceived general health. Therefore the Committee considered that DAS28 is the most applicable of the various measures of disease severity that could be readily applied in clinical practice.

4.3.5 The Committee noted that the licensed indications for all of the TNF-α inhibitors specified that patients should have active disease, and that previous NICE guidance and BSR guidelines (2005) defined active disease as a DAS28 score greater than 5.1. The Committee understood from clinical specialists that they would expect patients with approximately 8 to 10 swollen and tender joints to have a DAS28 greater than 5.1, which meant that in general, patients in the clinical studies had high levels of disease activity. The Committee therefore

concluded that it was appropriate to use the definition in the BSR guidelines (2005), which used a disease activity score (DAS28) of >5.1 measured on two occasions, 1 month apart, to confirm ongoing active RA.

4.3.6 The Committee discussed how best to define response to therapy. It noted that previous NICE guidance and BSR guidelines (2005) defined a response as an improvement in DAS28 score of greater than 1.2 or a fall to less than 3.2. The Committee heard from clinical specialists that this reflected a simplification of EULAR response criteria. The Committee noted that if treatment were initiated with DAS28 greater than 5.1 it would not be possible to get to below 3.2 unless there had been an improvement much greater than 1.2. The Committee therefore concluded that a response to therapy could be appropriately defined as a decrease in DAS28 greater than 1.2 alone.

4.3.7 The Committee considered how soon after the initiation of therapy it would be possible to identify a response. The clinical specialists advised that, in general, 3 months was long enough to determine whether a person's condition was likely to respond to treatment with TNF-α inhibitors, and that this was consistent with BSR guidelines (2005). However, the clinical specialists pointed out that this response criterion was reliant on the stability of other clinical factors, including comorbidities, for example concurrent infection and the use of other drugs such as steroids. The Committee was persuaded that although an initial DAS28 measurement would normally be taken 3 months after initiation of therapy, in the presence of the above clinical factors a further period of observation would often be considered appropriate. Overall the Committee concluded on the basis of both the clinical specialists' views and taking into account the need to ensure stability of other clinical factors, that in the absence of a clinical response at 6 months TNF-α inhibitor therapy should be discontinued.

4.3.8 The Committee carefully considered the economic modelling undertaken by the manufacturers, the BSR and the Assessment Group, and discussed the differences between the modelling strategies. It noted that the models had different structures, used different assumptions and that there were variations in the inputs used. The Committee considered that there were significant uncertainties relating to the assumptions in the models, most notably about

long-term disease progression and stabilisation while responding and not responding to TNF-α inhibitors and conventional DMARDs, and the effectiveness of conventional DMARDs in patients with established disease. The Committee noted that the models demonstrated varying sensitivities to these assumptions, particularly to disease progression. The Committee concluded that these factors introduced considerable uncertainty into the estimates of cost effectiveness in all the models.

4.3.9 The Committee was persuaded that the inclusion of benefits related to reduction in hospitalisations and longer-term requirements for joint replacement, although based on as yet unproven assumptions, was important in the economic modelling and an important factor to be taken into account in the costs associated with the treatment of RA. The Committee was however persuaded that this had been accounted for in the revisions to the Assessment Group model, and that this was not a key driver of the differences in cost effectiveness between the various models reviewed.

4.3.10 The Committee was aware of the limitations of using HAQ scores as a basis for estimating health-related quality of life in patients with RA. Namely that the HAQ is a measure of functional disability, which fails to capture the psychological and pain elements of quality of life associated with RA. In addition, the Committee noted that the HAQ scoring system may be an insensitive measure of small changes in health-related quality of life and may have a non-linear relationship to utility scores. The Committee noted that HAQ had been used as a basis for calculating utility across all the economic models, and while noting its limitations, accepted that it was the best means of estimating utility for the purposes of the economic analysis given the available data.

4.3.11 The Committee recognised that a key uncertainty, when assessing the cost-effectiveness of these technologies, related to whether there were differences in underlying HAQ progression between patients on treatment with TNF-α inhibitors and with conventional DMARDs. The Committee recognised that there were few data to inform estimates of long-term disease progression during treatment with the TNF-α inhibitors. It was aware there was evidence from open-label trial extensions which suggested that there was no

measurable HAQ progression while on TNF-α inhibitor therapy and that data from the BSR Biologics Register appeared to support this. However, it also recognised that the general population experienced some HAQ progression as it aged. Therefore, the Committee considered it appropriate to primarily examine the estimates of cost effectiveness based on the assumption of no HAQ progression while on TNF-α inhibitor therapy, while acknowledging the effects on the estimates of incorporating different assumptions of HAQ progression.

4.3.12 The Committee examined the estimates of cost effectiveness for third-line use of these agents (that is, after failure of two conventional DMARDs, including methotrexate) as recommended in previous NICE guidance and BSR guidelines (2005). It was aware that the Assessment Group had provided two estimates of cost effectiveness for TNF-α inhibitors for third-line use, one incorporating data from patients who were methotrexate naive (early RA) and one using data from patients for whom conventional DMARDs had failed (late RA). The Committee noted that estimates using the data from patients with early RA were more favourable but considered that this reflected an optimistic scenario, as none of the data came from trials of patients who had previously been unsuccessfully treated with two conventional DMARDs and a proportion of patients in the trials were DMARD naive. However, the Committee considered that the estimates of cost effectiveness for third-line use incorporating the data from people with late RA were likely to be conservative. The Committee concluded that in the economic modelling by the Assessment Group the true incremental cost effectiveness value was likely to lie between the results for the early and late RA data.

4.3.13 The Committee, having considered the third-line estimates from the Assessment Group, considered the estimates from the manufacturers and the BSR. It was aware of difficulties in comparing across models due to differences in the assumptions and data inputs, but noted that when the Assessment Group model was considered under the assumption of no HAQ progression, as had been used in the majority of the economic models submitted, the differences between the estimates of cost effectiveness from the manufacturers and the BSR and the Assessment Group were reduced. From the estimates of cost effectiveness the Committee concluded that, overall, the

use of these agents could be cost effective. However, because of the assumptions made about no disease progression while on TNF-α inhibitors, this would be dependent on maintenance of the initial response (defined in 4.3.6). The Committee therefore considered that response to treatment would need to be monitored at regular intervals. This should be carried out by a member of a specialist rheumatological team. TNF-α inhibitor therapy should be discontinued if an adequate response is not maintained.

4.3.14 The Committee was aware that the TNF-α inhibitors may also be used earlier in the treatment pathway as first- or second-line treatments. Considering first-line treatment, the Committee heard from clinical specialists that a large number of people in the early stages of disease initially respond well to conventional DMARDs, with methotrexate being considered particularly appropriate for those with poor prognostic factors. It noted current EULAR guidelines for the management of early RA, which recommended initial treatment with methotrexate, as well as BSR guidelines (2005), which recommended TNF-α inhibitor therapy after the failure of two conventional DMARDs. The Committee therefore concluded that patients should be prescribed methotrexate before they tried TNF-α inhibitors and that first-line use of these agents was not an appropriate use of NHS resources.

4.3.15 The Committee then considered the use of TNF-α inhibitors as a second-line therapy. It heard from clinical specialists that it was considered important that people had trials of conventional DMARDs soon after diagnosis of active disease and stopped them where the response was considered inadequate. The Committee heard that in clinical practice treatment was usually initiated with either methotrexate or sulfasalazine, with patients moving on to an alternative DMARD if the first was ineffective. The Committee heard that substantial numbers of patients with active RA obtain durable benefits from this approach. However, in some patients this could mean a quite rapid escalation of therapy to the use of TNF-α inhibitors after the failure of conventional DMARDs including methotrexate. Taking into consideration clinical practice and the uncertainties in the estimates of cost effectiveness of TNF-α inhibitors, the Committee was not persuaded that the use of TNF-α inhibitors after the failure of one conventional DMARD would be an appropriate use of NHS resources.

4.3.16 The Committee noted that treatment costs could vary across the three TNF-α inhibitors, and therefore considered that unless there were specific reasons for choosing one TNF-α inhibitor over another (for example, because of contraindications, mode of administration, or intolerance to treatment), therapy should be initiated with the drug that was least expensive (taking into account administration costs, required dose and product price per dose). Additionally, the Committee noted that in clinical practice dose escalation of these agents might be considered in order to maintain response, even if this is outside the current marketing authorisation. The Committee was not, however, persuaded that the extra benefits that might accrue from dose escalation would be justified by the extra costs and potential increase in adverse effects. The Committee therefore considered that dose escalation should not be recommended.

4.3.17 The Committee considered whether it was appropriate for a patient who experienced an adverse event soon after starting their first TNF-α inhibitor to be given an opportunity to consider trying a second. The Committee was aware of data from the BSR Biologics Register which suggested that such patients were more likely to also experience an adverse event to a second TNF-α inhibitor, but heard from clinical specialists that the reasons behind this were unclear. On balance the Committee considered that patients should be given the opportunity of responding to a TNF-α inhibitor. It concluded therefore that it was appropriate to recommend that an alternative TNF-α inhibitor be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.

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 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 rheumatoid arthritis and the doctor responsible for their care thinks that adalimumab, etanercept or infliximab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 NICE has developed tools to help organisations implement this guidance (listed below).

- A costing statement explaining the resource impact of this guidance.
- Audit criteria to monitor local practice.

6 Recommendations for further research

6.1 The Committee noted that there are a number of ongoing studies of etanercept, adalimumab and infliximab in people with RA, including direct comparisons between TNF-α inhibitors.

6.2 Further controlled clinical studies are required to assess the use of these drugs in combination with other therapies.

6.3 Evidence should be collected on the impact of TNF-α inhibitors on disease progression, joint replacement, mortality and quality of life, as assessed using a generic preference-based utility instrument (for example, the EQ-5D).

6.4 Further data collection is recommended from the current cohort enrolled in the BSR Biologics Register.

7 Related NICE guidance

- Rituximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 126 (2007). [Replaced by NICE technology appraisal guidance 195]
- Anakinra for rheumatoid arthritis. NICE technology appraisal guidance 72 (2006). [Replaced by NICE clinical guideline 79]
- Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. NICE technology appraisal guidance 35 (2002).
- Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs. NICE technology appraisal guidance 234 (2011).
- Rheumatoid arthritis. NICE clinical guideline 79 (2009).

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 was reviewed in January 2011. See the NICE website for details.

Andrew Dillon
Chief Executive
October 2007

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 Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley
Vice Chairman, InContact

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

Professor Mike Campbell
Statistician, University of Sheffield

Professor David Chadwick
Professor of Neurology, Walton Centre for Neurology and Neurosurgery

Dr Mark Chakravarty
Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd

Dr Peter I Clark
Honorary Chairman, Association of Cancer Physicians

Dr Mike Davies
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips
Public Affairs Manager, Medtronic Ltd

Professor Jack Dowie
Health Economist, London School of Hygiene

Dr Fergus Gleeson
Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch
Former Director of Nursing & Workforce Development, Mid Essex Services NHS Trust

Mr Sanjay Gupta
Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust

Professor Philip Home
Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Professor Peter Jones
Professor of Statistics & Dean Faculty of Natural Sciences, Keele University

Dr Mike Laker
Medical Director, Newcastle Hospitals NHS Trust

Dr George Levvy
Lay representative

Ms Rachel Lewis
Nurse Advisor to the Department of Health

Mr Terence Lewis
Mental Health Consultant, National Institute for Mental Health in England

Professor Jonathan Michaels
Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner
General Medical Practitioner, Sheffield

Dr Ruairidh Milne
Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

Dr Rubin Minhas
General Practitioner, Primary Care Cardiovascular Society

Mr Miles Scott
Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Professor Mark Sculpher
Professor of Health Economics, University of York

Dr Lindsay Smith
General Practitioner, East Somerset Research Consortium

Dr Ken Stein
Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, University of Birmingham

B. NICE project team

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

Zoe Garrett and Francis Ruiz
Technical Leads

Janet Robertson
Technical Adviser

Emily Marschke
Project Manager

Appendix B. Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by West Midlands HTA Collaboration, University of Birmingham.

- Chen Y-F, Jobanputra P, Barton P, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness, October 2005

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). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the FAD.

I) Manufacturer/sponsors:

- Abbot Laboratories Ltd
- Wyeth Pharmaceuticals
- Schering-Plough Ltd

II) Professional/specialist and patient/carer groups:

- Arthritis and Musculoskeletal Alliance
- Arthritis Care
- BackCare
- British Association of Spine Surgeons
- British Health Professionals in Rheumatology
- British Institute of Musculoskeletal Medicine
- British Orthopaedic Association
- British Society for Rheumatology

- Department of Health
- Eastern Hull Primary Care Trust
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Physicians
- Royal Pharmaceutical Society of Great Britain
- Somerset Coast Primary Care Trust
- Welsh Assembly Government

III) Commentator organisations (without the right of appeal):

- Arthritis Research Campaign
- Board of Community Health Councils in Wales
- British National Formulary
- National Public Health Service for Wales
- NHS Quality Improvement Scotland

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 the treatment of rheumatoid arthritis by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Robin Butler, Consultant Rheumatologist, Robert Jones and Agnes Hunt Orthopaedic Hospital, nominated by British Health Professionals in Rheumatology and British Society for Rheumatology – clinical specialist

- Dr Christopher Deighton, Consultant Rheumatologist, Derbyshire Royal Infirmary, nominated by the British Society for Rheumatology – clinical specialist
- Dr Frank McKenna, Consultant Physician and Rheumatologist, Trafford General Hospital, nominated by the British Society for Rheumatology – clinical specialist
- Mrs Ailsa Bosworth, Chair of the National Rheumatoid Arthritis Society, nominated by the National Rheumatoid Arthritis Society – patient expert
- Ms Homaira Khan, nominated by Arthritis Care – patient expert

Changes after publication

March 2014: implementation section updated to clarify that adalimumab, etanercept and infliximab are recommended as options for treating rheumatoid arthritis. Additional minor maintenance update also carried out.

March 2012: minor maintenance

About this guidance

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

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

It partially replaces 'Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 36) issued in March 2002.

This review and re-appraisal has additionally include adalimumab for the treatment of rheumatoid arthritis, and has taken into account changes in the marketing authorisations for infliximab and etanercept.

The Institute reviews each piece of guidance it issues.

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

Your responsibility

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

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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