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Etanercept and infliximab for the treatment of adults with psoriatic arthritis

NICE technology appraisal guidance 104 Etanercept and infliximab for the treatment of adults with psoriatic arthritis

Ordering information

You can download the following documents from www.nice.org.uk/TA104

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for people with psoriatic arthritis 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 the NHS Response Line on 0870 1555 455 and quote:

- N1092 (quick reference guide)
- N1093 ('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.

National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
London
WC1V 6NA

www.nice.org.uk

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1 Guidance

- 1.1 Etanercept, within its licensed indications, is recommended for the treatment of adults with severe active psoriatic arthritis only when the following criteria are met.
- The person has peripheral arthritis with three or more tender joints and three or more swollen joints.
 - The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs), administered either individually or in combination.
- 1.2 Etanercept treatment should be discontinued in patients whose psoriatic arthritis has not shown an adequate response when assessed using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. An adequate response is defined as:
- an improvement in at least two of the four PsARC criteria, one of which has to be joint tenderness or swelling score, with no worsening in any of the four criteria.
- 1.3 Infliximab, within its licensed indications, is recommended for the treatment of adults with severe active psoriatic arthritis if, under the circumstances outlined in section 1.1, treatment with an anti-TNF (tumour necrosis factor) agent is considered appropriate and the person has been shown to be intolerant of, or have contraindications to, treatment with etanercept or has major difficulties with self administered injections.
- 1.4 Infliximab treatment should be discontinued in patients whose psoriatic arthritis has not responded adequately at 12 weeks. An adequate response is defined in section 1.2.
- 1.5 It is recommended that the use of etanercept or infliximab for psoriatic arthritis should be initiated and supervised by specialist physicians experienced in the

diagnosis and treatment of psoriatic arthritis. If a person has both psoriatic arthritis and psoriasis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

2 Clinical need and practice

- 2.1 Psoriatic arthritis (PsA, psoriatic arthropathy) is an inflammatory arthritis closely associated with psoriasis. An estimated 5–7% of all people with psoriasis, and approximately 40% of those with extensive skin disease, have PsA. Undiagnosed PsA may be prevalent because many asymptomatic people with psoriasis have radiological evidence of joint damage.
- 2.2 The cause of PsA is not fully understood and there are no widely accepted diagnostic criteria. There is, however, considerable evidence for the role of the pro-inflammatory cytokine TNF released by T lymphocytes (T cells) and other inflammatory cells. PsA is generally diagnosed when a person with psoriasis presents with a distinctive pattern of peripheral or spinal arthropathy but does not test positive for rheumatoid factor (an antibody present in the blood of around 70% of people with rheumatoid arthritis [RA]). Fewer joints are affected with PsA than with RA, and the pattern of joint involvement is generally asymmetrical, involving the distal interphalangeal joints. In some patients there is spinal involvement (psoriatic spondylitis). The Moll and Wright classification, which is based on the joints affected, is commonly used to distinguish clinical subgroups of PsA. There is, however, overlap between the different forms, and the disease can evolve from one form to another.
- 2.3 Because of problems in definitively diagnosing PsA, there are few studies on its incidence and prevalence, and the results vary widely depending on the cohort studied and the diagnostic criteria used. PsA has a prevalence of between 0.1% and 1%. It affects men and women equally and its incidence peaks between the ages of 30 and 55 years.
- 2.4 Although PsA is a chronic progressive condition, its course may be erratic, with flare-ups and remissions. Symptoms can range from mild inflammation of

the synovial membrane surrounding a joint (synovitis) to severe progressive erosion of the joints. When the spine is affected the condition may be indistinguishable from ankylosing spondylitis.

- 2.5 The relationship between the skin and joint manifestations is unclear and the symptoms occur simultaneously in around 15% of people with the disease. In 60% of people the psoriasis precedes the arthritis. In 25%, the arthritis appears first. People with severe arthritis can have little or no skin disease, and vice versa. Flare-ups of symptoms do not necessarily coincide.
- 2.6 PsA can significantly impair a person's quality of life and cause disability; both skin and joints can be affected and people with PsA report more 'role limitation' and body pain than do people with RA. PsA also appears to be associated with an increased risk of premature mortality.
- 2.7 There are no commonly accepted criteria for the assessment of PsA and further work is ongoing. The PsARC is the only measure developed specifically for people with PsA. The PsARC comprises: a patient global self-assessment (on a 0–5 Likert scale); a physician global assessment (on a 0–5 Likert scale, with improvement defined as a decrease by at least 1 unit, and worsening defined as an increase by at least 1 unit); a tender joint score; and a swollen joint score (with improvement defined as a decrease of at least 30%, and worsening defined as an increase of at least 30%). The PsARC does not include an assessment of psoriasis. A PsARC response is defined as an improvement in at least two of the four measures, one of which must be the joint tenderness or swelling score, with no worsening in any of the four measures.
- 2.8 Clinical trials of treatments for PsA have mainly used outcomes validated in RA. It is recognised that RA outcomes may not sufficiently incorporate all aspects of disease activity and therefore clinical and radiological assessments remain important. The American College of Rheumatology (ACR) response criteria (ACR20, 50 and 70) require a specified reduction in tender joint count, swollen joint count, global assessments, pain, disability and an acute-phase

reactant. The Stanford Health Assessment Questionnaire (HAQ) is one component of the ACR criteria and scores physical disability from 0 (least disability) to 3 (most severe disability). Skin disease is usually monitored using the Psoriasis Area and Severity Index (PASI).

- 2.9 Treatment for PsA aims to improve the psoriasis or the arthritis, or both. The condition is managed by a number of specialties and there are reports of widespread variations in practice. Many drugs are used because they have demonstrated benefits in RA or psoriasis. As a result, the PsA evidence base is not well developed and there are few drugs that are specifically licensed for PsA. In early 2005, the British Society for Rheumatology issued a guideline on the use of anti-TNF- α therapy in PsA.
- 2.10 Mild PsA can be managed with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, with intra-articular corticosteroid injections when necessary. Topical therapies are used for the skin. DMARDs, including methotrexate, sulfasalazine, ciclosporin and leflunomide, are additionally used to reduce joint damage and limit disability. Gold compounds and anti-malarials are also used for PsA. Corticosteroids are used with caution because their withdrawal can trigger a flare-up of the psoriasis.

3 The technologies

3.1 *Etanercept*

- 3.1.1 Etanercept (Wyeth Pharmaceuticals) is a recombinant human TNF-receptor fusion protein. It interferes with the inflammatory cascade by binding to TNF, thereby blocking its interaction with cell-surface receptors. Etanercept is licensed for use in adults with active and progressive PsA that has responded inadequately to previous DMARDs. The number of previous DMARDs is not specified. Etanercept is also licensed for moderate to severe plaque psoriasis.

- 3.1.2 The Summary of Product Characteristics (SmPC) states that research into the long-term safety of combinations of etanercept with methotrexate is ongoing, and that the long-term safety of etanercept in combination with other DMARDs has not been established.
- 3.1.3 The most frequent adverse events reported during etanercept therapy include injection-site reactions, infections and allergic reactions. The SmPC specifies a number of uncommon but serious adverse events that may be related to the immunomodulatory activity. There are no monitoring requirements. For full details of side effects and contraindications, see the SmPC.
- 3.1.4 Etanercept is administered by subcutaneous injection at a dose of 25 mg twice weekly. The SmPC states that doses other than 25 mg twice weekly have not been studied. The net price for a 25-mg vial is £89.38 (excluding VAT; *British National Formulary*, 49th edition). Costs may vary in different settings because of negotiated procurement discounts.

3.2 *Infliximab*

- 3.2.1 Infliximab (Schering-Plough Ltd) is a chimeric monoclonal antibody that binds with high affinity to TNF, thereby neutralising its activity. It is licensed for the treatment of 'active and progressive PsA in patients who have responded inadequately to disease-modifying anti-rheumatic drugs'. The number of previous DMARDs is not specified. The SmPC specifies that infliximab must be taken with methotrexate. This is to limit the development of antibodies to infliximab and therefore reduce the risk of infusion reactions.
- 3.2.2 The most common adverse events reported during infliximab therapy include acute-infusion-related reactions, infections and delayed hypersensitivity reactions. The SmPC states that infliximab is contraindicated in people with moderate or severe heart failure, and before treatment is initiated, people must be screened for both active and inactive tuberculosis. The SmPC 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 SmPC.

- 3.2.3 Infliximab is administered at a dose of 5 mg/kg by intravenous infusion over 2 hours at weeks 0, 2 and 6, and thereafter every 8 weeks. The safety and efficacy of re-administration, other than every 8 weeks, has not been established. The net price for a 100-mg vial is £419.62 (excluding VAT; *Monthly Index of Medical Specialities*, April 2005). 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 (appendix B).

4.1 *Clinical effectiveness*

4.1.1 Etanercept

- 4.1.1.1 Two randomised controlled trials (RCTs, n = 265) were included in the Assessment Report. These trials were double-blind and placebo-controlled and were deemed to be of good quality by the Assessment Group. Neither trial required there to have been a failed response to DMARDs. In both RCTs, participants were allowed to have concomitant corticosteroids and NSAIDs. In addition, people were allowed DMARD monotherapy with methotrexate only. The controlled phase of both trials was followed by an open-label follow-up period during which the active drug was administered to all participants. The primary outcome in the 12-week smaller trial (n = 60) was PsARC response, whereas in the 24-week larger trial (n = 205) it was ACR20.

- 4.1.1.2 Etanercept was statistically significantly more effective than placebo for all arthritis outcomes in both RCTs, with the exception of the ACR70 in the smaller trial. In the subgroups of participants who also had at least 3% of their body surface area affected by psoriasis, the effect of etanercept was

statistically significantly greater than placebo as measured by the PASI 75 in both studies but not by the PASI 25 and PASI 50 at 12 weeks in the smaller RCT, and PASI 90 at 24 weeks in the larger RCT. The pooled results at 12 weeks showed a statistically significant difference in favour of etanercept in all outcomes apart from PASI 75, and no statistical heterogeneity was detected: PsARC relative risk [RR] 2.6 (95% confidence interval [CI], 2.0 to 3.5); ACR50 RR 10.8 (95% CI, 4.5 to 26.3); PASI 75 RR 2.3 (95% CI, 0.9 to 6.0); PASI 50 RR 2.4 (95% CI, 1.4 to 4.2); HAQ 49% change from baseline (95% CI, 38.5 to 59.4). The 24-week results in the larger RCT were: PsARC RR 3.0 (95% CI, 2.1 to 4.4); ACR50 RR 9.5 (95% CI, 3.5 to 25.8); PASI 75 RR 7.0 (95% CI, 1.7 to 29.6); HAQ 47% change from baseline (95% CI, 32.5 to 61.9). In the larger RCT, the Total Sharp Score radiographic assessment that measures annualised rate of progression at 24 weeks was statistically significantly lower in the group that had received etanercept than in the group that had received placebo.

4.1.1.3 In the larger RCT, subgroup analysis by concomitant methotrexate treatment (stratified at randomisation) indicated that the effect of etanercept did not depend on the concomitant use of methotrexate. The uncontrolled follow-up data reflected those in the controlled period and the 1-year Total Sharp Score data indicated that, on average, there was no clinically significant disease progression.

4.1.1.4 In the larger RCT, at 24 weeks 65 of the 101 participants receiving etanercept experienced an adverse event (64%) compared with 69 of the 104 participants in the placebo group (66%) (RR 1.0; 95% CI, 0.8 to 1.2). Four people in each group experienced serious adverse events (RR 1.0; 95% CI, 0.3 to 4.0) and one person in each group withdrew because of adverse events (RR 1.0; 95% CI, 0.1 to 16.2).

4.1.2 Infliximab

4.1.2.1 One RCT (the infliximab multinational psoriatic arthritis controlled trial, or IMPACT) was included in the Assessment Report and deemed to be of good

quality. All 104 participants had to have had PsA that had failed to respond to at least one DMARD. People were allowed to have concomitant corticosteroids and NSAIDs plus DMARD monotherapy with any agent. The controlled phase of the RCT was followed by an open-label follow-up period during which the active drug was administered to all participants.

4.1.2.2 The primary outcome measure in the RCT was ACR20. At 16 weeks the people taking infliximab had a statistically significant improvement in ACR20 compared with those taking placebo (34/52 [65%] of the treatment group achieved ACR20 compared with 5/52 [10%] of the placebo group [RR 6.8; 95% CI, 2.9 to 16.0]). In addition, 24/52 (46%) of the group that had received infliximab achieved an ACR50 response compared with 0% of the placebo group (RR 49.0; 95% CI, 3.1 to 785.1), and 15/52 (29%) achieved an ACR70 response compared with 0% in the placebo group (RR 31.0; 95% CI, 1.9 to 504.9). In terms of PsARC response, 39/52 (75%) patients in the treatment group achieved a response compared with 11/52 (21%) in the placebo group (RR 3.55; 95% CI, 2.05 to 6.13).

4.1.2.3 The results of radiographic assessments of joint disease in the infliximab trial have been published in abstract form. They suggest that at week 50, the total radiographic score had not worsened in 84% of the participants who had received infliximab for the whole period.

4.1.2.4 In total in the IMPACT RCT, 38 of the 52 people in the infliximab group experienced an adverse event (73%) compared with 33 of the 51 people in the placebo group (65%) (RR 1.1; 95% CI, 0.9 to 1.5). Serious adverse events were experienced by one person in each group (RR 1.0; 95% CI, 0.1 to 15.3). Two people in the infliximab group withdrew because of adverse events compared with one person in the placebo group (RR 2.0; 95% CI, 0.2 to 21.4).

4.1.2.5 The results of IMPACT 2 have recently been published. Two hundred patients with active PsA unresponsive to previous treatment were randomised to infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 14

and 22. All participants had to have shown an inadequate response to current or previous DMARDs or NSAIDs. Concomitant methotrexate and oral corticosteroid use was permitted in the trial.

- 4.1.2.6 The primary outcome measure in IMPACT 2 was ACR20 at 14 weeks. At 24 weeks the people taking infliximab had a statistically significant improvement in ACR20 compared with those taking placebo (54/100 [54%] of the treatment group achieved ACR20 compared with 16/100 [16%] of the placebo group [RR 3.37; 95% CI, 2.08 to 5.48]). In addition, 41% (41/100) of the group that had received infliximab achieved an ACR50 response compared with 4% of the placebo group (RR 10.25; 95% CI, 3.81 to 27.55), and 27% (27/100) achieved an ACR70 response compared with 2% in the placebo group (RR 13.5; 95% CI, 3.29 to 55.26).
- 4.1.2.7 In terms of PsARC response, 70/100 (70%) patients in the treatment group achieved a response, compared with 32/100 (32%) in the placebo group (RR 2.19; 95% CI, 1.59 to 2.99). In the subgroups of participants who also had at least 3% of their body surface area affected by psoriasis, the effect of infliximab was statistically significantly greater than that of placebo as measured by the PASI 50 (RR 9.3; 95% CI, 4.5 to 19.1), PASI 75 (RR 52.4; 95% CI, 7.4 to 370.1) and PASI 90 (RR 68.1; 95% CI, 4.2 to 1094.7).
- 4.1.2.8 In total, by week 24, 100 of the 150 people in a combined group of patients who received infliximab (including those who were randomised to placebo but entered an early escape at week 16 and received infliximab, and those in the placebo group who incorrectly received infliximab) experienced an adverse event (67%) compared with 65 of the 97 people in the placebo group (67%) (RR 0.9; 95% CI, 0.8 to 1.2). Serious adverse events were experienced by 6 people in the placebo group and 13 in the combined infliximab group (RR 1.4; 95% CI, 0.6 to 3.6). Six people in the combined infliximab group withdrew because of adverse events compared with one in the placebo group (RR 3.9; 95% CI, 0.5 to 31.7).

4.2 Cost effectiveness

4.2.1 Published economic evaluations

4.2.1.1 The Assessment Group did not identify any published economic evaluations of either etanercept or infliximab in PsA.

4.2.2 Etanercept – manufacturer’s model

4.2.2.1 The manufacturer of etanercept developed an individual patient-level simulation in their modelling approach using data from one of the RCTs. HAQ scores were used to derive utility gains and estimate the cost of treatments. It was assumed that DMARD treatment with methotrexate and sulfasalazine would have failed before etanercept was considered. People with PsA that failed to respond to etanercept would then be treated with ciclosporin in combination with methotrexate, or leflunomide alone, followed by supportive care on failure. The comparator was the same treatment sequence without etanercept. Costs and benefits were both discounted at 3.5%. The impact of adverse events on costs and utility were not considered in the modelling.

4.2.2.2 Results were presented for four alternative time horizons: 6 months, 2 years, 5 years and 10 years. In the base case, the cost per quality-adjusted life year (QALY) gained for etanercept declined as the time horizon increased, ranging from around £66,590 for a 6-month time horizon to £28,190 for a 10-year time horizon. A Monte Carlo simulation under base-case assumptions and a time horizon of 10 years indicated that 58% of the cost-effectiveness estimates fell below a willingness-to-pay threshold of £30,000, whereas 5% were below £20,000. Univariate sensitivity analyses generated incremental cost-effectiveness ratios (ICERs) ranging from around £35,220 per QALY to £17,200 with a 10-year time horizon.

4.2.3 Infliximab – manufacturer’s model

4.2.3.1 The manufacturer of infliximab developed two Markov models, with the comparator being ‘standard supportive therapy’ only. One model – the

Active Joint Model – considered only the short-term effect of flare-ups of active joints, whereas the second – the Chronic Active Joint Model – included this short-term effect but also modelled how flare-ups contribute to the long-term development of deformed joints. The key effectiveness parameters in the models were taken from the IMPACT trial and from an observational study (the Toronto Psoriatic Arthritis Research Program), which also supplied the estimates for utility (based on EQ-5D) and resource use. Disease progression, non-drug costs and people’s responses to treatment were based on the number of active joints. The cost analysis within the model (except the drug costs) was based on resource use estimates from Canada rather than from the NHS. Costs and benefits were both discounted at 3.5%.

4.2.3.2 The models were analysed as ‘first-order’, patient-level simulations comprising 1000 iterations. The analyses used a cost of infliximab of £451.20 per 100-mg vial. The base-case results of the Active Joint Model gave an ICER of infliximab over supportive care of approximately £37,000 (5-year time horizon). The discount rate and time horizon were varied in the sensitivity analyses. Different discount rates appeared to have minimal impact on the ICER of infliximab over supportive care. Two-year, 10-year and 30-year time horizons gave ICERs of around £58,600 (95% CI, £37,660 to £156,460), £33,300 (95% CI, £28,760 to £38,900) and £31,100 (95% CI, £29,640 to £35,840), respectively.

4.2.3.3 In the case of the Chronic Active Joint Model, the ICER in the base-case scenario was around £33,900 (30-year time horizon). Five-year, 10-year and 45-year time horizons gave ICERs of around £41,100 (95% CI, £29,990 to £56,390), £37,400 (95% CI, £28,320 to £46,750) and £35,300 (95% CI, £24,780 to £53,160), respectively.

4.2.4 The Assessment Group model

4.2.4.1 The Assessment Group developed a cohort model, which examined the cost effectiveness of etanercept, infliximab and supportive care (that is, therapy

excluding DMARDs and anti-TNFs). It was assumed that these would be the relevant treatment options for people with PsA that had not responded to any DMARD available. Adverse events were not considered in the modelling.

- 4.2.4.2 The Assessment Group model used short-term trial data (based on a Bayesian evidence synthesis) to model the response of people to anti-TNF therapy at 12 weeks based on PsARC. For those whose condition responded, there was an ongoing risk that they would withdraw from treatment at any time-point. An estimate of annual withdrawal rate was therefore also incorporated into the model. The long-term withdrawal rate was based on a 2-year non-randomised observational study in RA, and assumed a constant rate of withdrawal and no difference between the two biological therapies. People for whom treatment failed at any time-point were assumed to move on to supportive care.
- 4.2.4.3 As in the manufacturer's model for etanercept, disability from PsA, as measured by HAQ score, was used as a basis for determining both health-related quality of life (in terms of utility) and the costs of treatment (excluding the unit costs of the biological therapies). People who responded to biological therapy experienced an initial decrease in HAQ score, and a slower progression rate with no further increase in HAQ. The HAQ score of people who failed to respond to biological therapy after the initial 12-week period rebounded, with one of two alternative scenarios. In the best-case scenario after an initial response to therapy failed, the person's HAQ score rebounded equal to the gain and then increased at the same rate as it would with natural progression. In the worst-case scenario when therapy failed, the person's HAQ returned to the level and subsequent trajectory at which it would have been had he or she not initially responded to therapy (that is, the increase in HAQ score on failure of therapy exceeded the initial drop).
- 4.2.4.4 In the analysis, four alternative time horizons were considered: 1 year, 5 years, 10 years and 40 years (lifetime), and uncertainty was explored by

probabilistic sensitivity analysis. Under the best-case rebound scenario, the incremental cost, per QALY gained, of etanercept compared with palliative care ranged from £14,820 (women, 40-year time horizon) to £49,370 (men, 1-year time horizon). Under the second, worst-case rebound scenario, the ICERs were higher, ranging from £25,440 (women, 40-year time horizon) to £49,440 (men, 1-year time horizon). The probabilistic sensitivity analysis showed that etanercept and palliative care had the highest probabilities of being cost effective at a threshold of £30,000 per QALY gained.

- 4.2.4.5 The Assessment Group's base case model showed that infliximab was consistently dominated by etanercept because of its higher acquisition and administration costs (infliximab did not demonstrate superior effectiveness). This was the case for both rebound scenarios. When etanercept was removed from the comparison, the ICER of infliximab versus supportive care ranged from £21,380 (women, rebound equal to gain, 40-year time horizon) to £90,790 (men, rebound to natural history, 1-year time horizon).
- 4.2.4.6 A scenario analysis was also undertaken to examine the impact of allowing the HAQ score of responders to etanercept and infliximab to increase at the same rate as natural progression after the initial HAQ decrease. Under this assumption the ICER of etanercept for men over a 10-year time horizon was around £44,600 (base case = £30,400 under the 'worst-case' rebound scenario).
- 4.2.4.7 In addition, the Assessment Group undertook a number of sensitivity analyses relating to the base-case estimates of the effectiveness of infliximab and etanercept (based on PsARC response rates at 12 weeks), the average number of vials of infliximab used in any one infusion, and the non-drug cost of administering infliximab. With the exception of the analysis relating to PsARC response rates, infliximab remained dominated by etanercept in these analyses, even when the non-drug administration costs of infliximab were reduced by more than half.

4.2.4.8 The Assessment Group explored the possibility that there is a better treatment response rate with infliximab in terms of PsARC than was originally estimated in the evidence synthesis. This was done by introducing an alternative prior specification for the study effects: the PsARC response rate at 12 weeks for infliximab was increased to 84% (from 77%) and the PsARC response rate to etanercept was reduced to 73% (from 77%). In terms of cost effectiveness, infliximab was no longer dominated by etanercept, but the ICERs were in excess of £84,000 with a 40-year time horizon (males) and greater than £165,000 with a 10-year time horizon (males).

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of etanercept and infliximab, having considered evidence on the nature of the condition and the value placed by users on the benefits of etanercept and infliximab from people with PsA, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.

4.3.2 The Committee noted that the effects of etanercept and infliximab on the inhibition of TNF and the adverse events in studies were similar. Additionally, they accepted that the RCTs demonstrated the efficacy of etanercept and infliximab in people with PsA. The Committee noted, however, that all relevant RCTs were of comparatively short duration and that the sample sizes were generally small. It also noted that the inclusion criteria did not perfectly reflect the population for which these technologies are currently licensed. In particular, in the etanercept RCTs, previous DMARD use was not a requirement for enrolment and IMPACT 2 patients had to have had an inadequate response to either DMARDs or NSAIDs. Expert testimony and analysis of the baseline characteristics of the people included in all the trials, however, suggested that the participants

nevertheless represented a population with relatively severe PsA similar to those currently being treated in clinical practice after DMARD failure.

- 4.3.3 The Committee carefully considered the economic modelling undertaken by the manufacturers and the Assessment Group. It discussed the differences between the modelling strategies and acknowledged their respective merits. It noted the varying time horizons employed in the economic analyses and concluded that although the nature of the condition indicated a potential for long-term benefit from treatment, the short-term trial data currently available meant that it could not confidently support a modelling perspective of greater than 10 years. In addition, the Committee noted the experts' concerns regarding the limited clinical experience with these agents in the management of PsA and the balance between benefits and risks in the longer term.
- 4.3.4 The Committee noted that none of the economic models took into account the likely benefits of etanercept and infliximab on the psoriasis component of the disease, and therefore they may have underestimated the relative cost effectiveness of both interventions. The Committee was aware of the limitations of using HAQ scores as a basis for determining health-related quality of life in patients with PsA treated with these agents. Nevertheless, having considered the sensitivity analyses undertaken, which included more than halving the non-drug administration costs of infliximab and increasing the effectiveness of infliximab (see Section 4.2.4.8), the Committee concluded that treatment with etanercept would be more cost effective than treatment with infliximab.
- 4.3.5 The Committee, however, recognised the benefits of both of these agents and noted that certain subgroups of patients who would not be suitable for treatment with etanercept might benefit from treatment with infliximab. The Committee was persuaded that infliximab should be a treatment option in the circumstances where the use of an anti-TNF agent is considered appropriate in a person with PsA (under the criteria outlined in section 1.1),

but where the individual has been shown to be intolerant of, or have contraindications to, treatment with etanercept.

- 4.3.6 The Committee did not think it appropriate to recommend that a person who did not respond adequately to etanercept (as defined in Section 1.2) should be treated with infliximab. This was due to the absence of data to demonstrate that a person with PsA failing etanercept treatment would benefit from treatment with infliximab. The Committee understood that the British Society for Rheumatology's Biologics Register was collecting data on sequential use of the anti-TNFs, principally in patients with rheumatoid arthritis. It concluded that such data where relevant should be considered when the current guidance is reviewed.
- 4.3.7 The Committee further considered issues of concordance with medication related to the different modes of administration of etanercept and infliximab. It was not persuaded by the evidence presented that concordance with treatment would be significantly affected by the different modes of administration of these two agents to a degree that would outweigh the evidence of the cost-effectiveness analysis. The Committee did however appreciate the argument that major difficulties with self-administered injections, for example because of coexisting severe psoriasis, could make this mode of use inappropriate, and infliximab should therefore be considered a treatment option (under the criteria outlined in section 1.1).
- 4.3.8 The Committee was mindful that the licensed indications for both etanercept and infliximab state that patients must have active and progressive PsA and that there must have been an inadequate response to at least one previous DMARD. However, it accepted the definition of active joint disease and DMARD failure used in the British Society for Rheumatology guidelines as: people must have active joint disease (at least three tender joints and at least three swollen joints) and have failed to respond to adequate therapeutic trials of at least two standard DMARDs.

- 4.3.9 The Committee considered, on the basis of the trials, that there was no evidence to differentiate between treatment options for mono, oligo or polyarthritis in people with PsA. In addition, it was persuaded in discussion with the clinical experts that evidence for the clinical effectiveness of etanercept and infliximab in people with spinal arthropathy was much less convincing than for peripheral arthritis principally because of under-representation of people with axial disease in the trials.
- 4.3.10 The Committee discussed the most appropriate method of assessing response to treatment with the anti-TNFs in clinical practice and the time after initiation of therapy that this should be undertaken. The Committee was aware of the limitations of the PsARC measurement criteria, but was persuaded by the clinical experts that PsARC was the most applicable of the possible outcome measures that could be readily used in clinical practice. The Committee further noted the similarity in the numbers of people responding at 12 and 24 weeks in the larger of the etanercept trials, and in the numbers responding at 14 and 24 weeks in the larger of the infliximab trials. The experts advised that 12 weeks was long enough to determine whether a person's condition was likely to respond to treatment with either etanercept or infliximab. Therefore, the Committee concluded that etanercept should be discontinued if a PsARC response (as defined in Section 2.7) was not achieved at 12 weeks after initiation of therapy. In addition, in the circumstances in which infliximab was to be used, the same criteria should be applied.
- 4.3.11 The Committee acknowledged that there was the possibility of severe side effects with etanercept and infliximab and that there was little information on the use of these drugs in people with PsA beyond the duration of the RCTs. It was also aware that these drugs could increase the risk of malignancy and that people with PsA were potentially already at an increased risk of skin cancer because of therapeutic exposure to ultraviolet radiation for psoriasis. Consequently, the Committee was of the strong opinion that all people treated with etanercept and infliximab for PsA should be included in a

registry to enable ongoing collection of information on long-term outcomes including adverse effects. The Committee considered that cross-referencing (with a psoriasis registry) of the data for people treated for psoriasis and PsA would be necessary to ensure that all information on the use of these agents was captured. The Committee reached the view that treatment with etanercept and infliximab should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of PsA. Additionally, if a person has both PsA and psoriasis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

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/TA104).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit criteria to monitor local practice (see appendix C).

6 Recommendations for further research

6.1 The Committee noted that there are a number of ongoing studies of etanercept and infliximab in people with PsA. However, it stressed that efficacy trials conducted in the specific population for which etanercept and infliximab are licensed are required (people with active and progressive PsA that has responded inadequately to one or more DMARDs). In addition, these trials should be of adequate duration and compare etanercept and infliximab with each other and with other treatments for PsA. Information should also be collected on the use of these drugs in combination with other therapies.

6.2 There is a national register held by the British Society for Rheumatology that collects data on the use of cytokine inhibitors in people with RA. Although some people with PsA are included, the Committee was of the opinion that more should be enrolled. This would facilitate the collection of information on long-term outcomes, including joint disease progression. It would also potentially assist the identification of subgroups of people who respond better to these treatments and people who respond better to cytokine inhibitors with a particular mechanism of action.

6.3 Further research is needed into the impact of cytokine inhibitors both on the arthritic and the skin components of the disease, and their impact on quality of life as assessed using a generic preference-based utility instrument.

7 Related guidance

- 7.1 All issued guidance and details of appraisals and guidelines in progress are available on the NICE website (www.nice.org.uk).
- 7.2 Etanercept and efalizumab for the treatment of adults with psoriasis. *NICE technology appraisal guidance* no. 103 (2006). Available from www.nice.org.uk/TA103

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 any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.
- 8.2 The guidance on these technologies will be considered for review in 1 year.

Andrew Dillon
Chief Executive
July 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE 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 twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. 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.

Ms Julie Acred

Chief Executive Officer, Derby Hospitals

Dr Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences,
University of Manchester

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care and Honorary Senior Lecturer, Department of Child Health, Leicester Royal Infirmary

Mr Brian Buckley

Vice Chairman, InContact

Professor Mike Campbell

Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Mark Chakravarty

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd, Egham, Surrey

Dr Peter I Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Wirral, Merseyside

Ms Donna Covey

Chief Executive, Asthma UK

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

Professor Gary A Ford (Vice Chair)

Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Dr Fergus Gleeson

Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch

Former Director of Nursing, Mid-Essex Hospital Services NHS Trust, Chelmsford

Professor Trisha Greenhalgh

Professor of Primary Health Care, University College London

Miss Linda Hands

Clinical Reader in Surgery, University of Oxford

Professor Peter Jones

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

Professor Robert Kerwin

Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology Assessment, University of Southampton

Dr Neil Milner

General Medical Practitioner, Sheffield

Dr Rubin Minhas

General Practitioner with a Special Interest in Coronary Heart Disease, Primary Care CHD Lead, Medway PCT & Swale PCT

Mr Miles Scott

Chief Executive, Harrogate Health Care NHS Trust

Professor Mark Sculpher

Professor of Health Economics, University of York

Dr Ken Stein

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

Professor Andrew Stevens

Professor of Public Health, University of Birmingham

Ms Jayne Wilson

Systematic Reviewer, WMHTAC, Department of Public Health and Epidemiology

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Sarah Garner

Technical Lead, NICE project team

Francis Ruiz

Technical Lead, NICE project team

Emily Marschke

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the Centre for Reviews and Dissemination/Centre for Health Economics, University of York.

Woolacott N, Bravo Y, Hawkins N, et al. *Etanercept and infliximab for the treatment of psoriatic arthritis*. February, 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, the assessment report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Wyeth Pharmaceuticals
- Schering-Plough Ltd

II Professional/specialist and patient/carer groups:

- Arthritis and Musculoskeletal Alliance
- British Association of Dermatologists
- British Society for Rheumatology
- Department of Health
- Primary Care Dermatology Society
- Psoriatic Arthropathy Alliance
- The Psoriasis Association
- Royal College of Nursing
- Royal College of Physicians
- Royal Pharmaceutical Society
- Skin Care Campaign

III Commentator organisations (without the right of appeal):

- British National Formulary
- National Public Health Service for Wales
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Welsh Assembly Government

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on etanercept and infliximab for the treatment of PsA by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Philip Helliwell, Senior Lecturer, Rheumatology, British Society for Rheumatology
- Mr David Chandler, External Affairs, Psoriatic Arthropathy Alliance
- Ms Gladys Edwards, Chief Executive, the Psoriasis Association

Appendix C. Detail on criteria for audit of the use of etanercept and infliximab for the treatment of adults with psoriatic arthritis

Possible objectives for an audit

An audit could be carried out to ensure that etanercept and infliximab are used appropriately in the treatment of PsA.

Possible patients to be included in the audit

An audit could be carried out on all adults seen for PsA in a reasonable period for audit, for example 6 months.

An alternative could be to find patients for whom etanercept or infliximab has been prescribed as treatment for PsA, and use the measures below to ensure that the drugs have been prescribed appropriately.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of etanercept and infliximab for the treatment of PsA are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. An adult with severe active psoriatic arthritis (PsA) is prescribed etanercept, within its licensed indications, only when the following criteria are met.</p> <p>a. The person has peripheral arthritis with ≥ 3 tender joints and ≥ 3 swollen joints and</p> <p>b. The PsA has not responded to adequate trials of at least two standard DMARDs administered either individually or in combination</p>	<p>100% of adults with severe active PsA who are prescribed etanercept</p>	<p>None</p>	<p>'Disease modifying anti-rheumatic drugs (DMARDs)' include methotrexate, sulfasalazine, ciclosporin and leflunomide. As a guide for designing the audit, see the British Society for Rheumatology Guidelines for anti-TNF-α therapy in psoriatic arthritis for more detail related to definitions. These define an adequate trial of at least two standard DMARDs as treatment for at least 6 months, of which at least 2 months is at standard target dose (unless significant intolerance or toxicity limit the dose), or treatment for < 6 months, where treatment was withdrawn because of drug intolerance or toxicity, but normally after at least 2 months at therapeutic doses</p>
<p>2. An adult with severe active PsA is prescribed infliximab, within its licensed indications, only when all of the following criteria are met</p>	<p>100% of adults with PsA who are prescribed infliximab</p>	<p>None</p>	<p>See above for relevant definitions. Clinicians will need to agree locally on how to measure the judgement that treatment with an anti-TNF agent is considered</p>

<p>a. The person has peripheral arthritis with ≥ 3 tender joints and ≥ 3 swollen joints and</p> <p>b. The PsA has not responded to adequate trials of at least two standard DMARDs administered individually or in combination and</p> <p>c. Treatment with an anti-TNF (tumour necrosis factor) agent is considered appropriate and</p> <p>d. The person has been shown to be intolerant of, or have contraindications to, treatment with etanercept or has major difficulties with self administered injections, due to severe psoriasis</p>			<p>appropriate and the signs and symptoms that indicate that a person has been shown to be intolerant of, or have contraindications to, treatment with etanercept or has major difficulties with self administered injections</p>
<p>3. The response to etanercept or to infliximab is assessed after 12 weeks of treatment</p>	<p>100% of people for whom etanercept or infliximab has been prescribed for PsA and who have been on the drug for at least 12 weeks</p>	<p>None</p>	<p>Clinicians will need to agree locally on how assessment of response to treatment is documented, for audit purposes. Assessment must include use of the Psoriatic Arthritis Response Criteria (PsARC)</p>
<p>4. The prescription of etanercept or infliximab is discontinued unless the PsA has shown a response to treatment</p>	<p>100% of people for whom etanercept or infliximab has been prescribed for PsA and</p>	<p>None</p>	<p>'A response to treatment' is defined as an improvement in at least two of the four PsARC criteria, one of which has to be joint tenderness or swelling score,</p>

	who have been on the drug for at least 12 weeks		with no worsening in any of the four criteria
5. The use of etanercept or infliximab is initiated and supervised by a specialist physician experienced in the diagnosis and treatment of PsA	100% of people for whom etanercept or infliximab has been prescribed for PsA	A. If a person has both PsA and psoriasis, his or her treatment is managed by collaboration between a rheumatologist and a dermatologist	Clinicians will need to agree locally on what constitutes initiation and supervision of the use of etanercept or infliximab for PsA and what constitutes collaboration between a rheumatologist and a dermatologist, for audit purposes

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **criterion plus** number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.