

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final Appraisal Determination

### Efalizumab and etanercept for the treatment of adults with psoriasis

#### 1 Guidance

- 1.1 Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met.
- The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] of ten or more **and** a Dermatology Life Quality Index [DLQI] of more than ten.
  - The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.
- 1.2 Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either:
- a 75% reduction in the PASI score from when treatment started (PASI 75) or
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.

- 1.3 Efalizumab, within its licensed indications, is recommended for the treatment of adults with plaque psoriasis under the circumstances detailed in Section 1.1 only if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of, or have contraindications to, treatment with etanercept.
- 1.4 Further treatment with efalizumab is not recommended in patients unless their psoriasis has responded adequately at 12 weeks as defined in Section 1.2.
- 1.5 It is recommended that the use of etanercept and efalizumab for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.
- 1.6 Patients who have begun a course of treatment with efalizumab at the date of publication of this guidance should have the option of continuing to receive treatment until the patients and their clinicians consider it is appropriate to stop.

## **2 Clinical need and practice**

- 2.1 Psoriasis is an inflammatory skin disease that is characterised by an accelerated rate of turnover of the top layer of the skin (epidermis). Although it is a chronic progressive condition, its course may be erratic, with flare-ups and remissions.
- 2.2 The cause of psoriasis is not fully understood but evidence suggests that there is a strong genetic component and that it is mediated by abnormal T lymphocytes. Environmental factors also play a role, and it has been established that in some cases factors such as emotional stress or infection may trigger the first episode of psoriasis and may also cause exacerbations. Some medications may also cause exacerbations.

- 2.3 The most common form (80%) of psoriasis is chronic plaque psoriasis (psoriasis vulgaris), which is characterised by well-demarcated, often symmetrically distributed, thickened, red, scaly plaques. There is considerable variation in both the size and the number of the plaques, which can range from one or two small plaques to 100% body coverage. Although the plaques can affect any part of the skin, they are typically found on the extensor surfaces of the knees and elbows, and on the scalp. It is estimated that 5–7% of all people with psoriasis, and approximately 40% of those with extensive skin disease, develop joint inflammation, which is known as psoriatic arthritis (PsA).
- 2.4 There are few data on the prevalence and incidence of psoriasis in the UK but estimates suggest that it affects approximately 2% of the population. Males and females are affected equally by the condition and there is a higher incidence in white people than in members of other ethnic groups.
- 2.5 A UK study of people with severe psoriasis found that 60% had taken time off work in the previous year as a direct result of their condition. People with severe disease may require a number of hospitalisations each year; the average length of a hospital stay is around 20 days.
- 2.6 Psoriasis is generally graded as mild, moderate or severe. Several different scales for measuring the severity of psoriasis are also used, which are variably based on the following criteria: the proportion of body surface area affected; the disease activity (degree of plaque redness, thickness and scaling); the response to previous therapies; and the impact of the disease on the person.
- 2.7 The Psoriasis Area Severity Index (PASI) is the most widely used measurement tool for psoriasis in clinical trials. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease). A PASI score of more than ten has been shown to correlate with a number of indicators commonly associated with severe disease such as the need for hospital admission. Trial

outcomes are generally reported in terms of the number of people reaching a specified percentage reduction in PASI from their baseline score (for example, PASI 75 is a 75% reduction from baseline score). The European Medicines Agency (EMA) recognises the achievement of a PASI 75 as an indicator in clinical trials that severe psoriasis has responded to treatment.

- 2.8 Psoriasis has been shown to affect health-related quality of life (HRQoL) to an extent similar to the effects of other chronic diseases such as depression, myocardial infarction, hypertension, congestive heart failure or type 2 diabetes. In general, increased severity of psoriasis is associated with decreased HRQoL. However, the degree of this effect on quality of life is also dependent on the area of the body affected by psoriasis. Thus, even mild psoriasis in the flexures or exposed areas such as the face can be very distressing. The Dermatology Life Quality Index (DLQI) is a validated HRQoL measure that consists of ten questions covering symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. Scores range from 0 (best HRQoL) to 30 (worst possible HRQoL). A score of greater than 10 is considered to correlate with a substantial effect on a person's HRQoL.
- 2.9 There is no cure for psoriasis but there is a wide range of topical and systemic treatments that can potentially manage the condition. Most treatments, however, only reduce the severity rather than stop the episodes, and the psoriasis therefore has to be treated continually and on a long-term basis. The choice of treatment depends on a number of factors including the severity of the condition and the extent of body surface area affected. In general, the evidence base for many of these therapies is not well developed.
- 2.10 Mild to moderate psoriasis, particularly when a limited area of skin is involved, can be managed with topical treatments, including emollients and occlusive dressings, keratolytics (salicylic acid), coal tar, dithranol, corticosteroids, retinoids and vitamin D analogues. The burden for the person with psoriasis

can be considerable as many of the preparations have a strong smell, are messy and require application two or three times a day.

- 2.11 More severe, resistant and/or extensive psoriasis can be treated with photo(chemo)therapy, acitretin (an oral retinoid) and oral drugs that act on the immune system, such as ciclosporin, methotrexate and hydroxycarbamide. Oral treatments can be given alone or in conjunction with topical therapies. All the oral therapies have the potential to cause severe long-term side effects, and monitoring is required. The toxic effects are cumulative and therefore many people with psoriasis require 'rotational therapy' in order to minimise the cumulative toxicity of any one treatment.
- 2.12 There is very little information on current practice in treating psoriasis in the NHS and it is likely that there are widespread variations in service. There are also few data on the current service costs; nearly 1 million prescriptions for psoriasis therapies were dispensed in 2003 at a cost of £27.8 million. This does not include treatments that are also used for other conditions (for example, corticosteroids or methotrexate) or costs associated with treatment in secondary or tertiary care. Excluding drug costs, mean costs for inpatient care have been estimated at £5215 per patient.

### **3 The technologies**

#### **3.1 *Efalizumab***

- 3.1.1 Efalizumab (Serono Pharmaceuticals Ltd) is a T-cell modulator that blocks T-cell activation or migration. It is licensed for the 'treatment of adults with moderate to severe plaque psoriasis who have failed to respond to, or who have a contraindication to, or who are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA'. The UK marketing authorisation for efalizumab also specifies that the psoriasis should be chronic, and it is contraindicated in patients with specific forms of psoriasis like guttate, erythrodermic or pustular psoriasis as the sole or predominant form.

- 3.1.2 The 'Summary of Product Characteristics' (SPC) states that efalizumab treatment should be initiated by a physician specialised in dermatology. The SPC states that efalizumab has not been studied in combination with immunosuppressive systemic anti-psoriasis medicinal products and therefore combination therapy with these products is not recommended. The SPC also states that 'combination therapy with topical corticosteroids is not associated either with any untoward effects or with any observable significant benefit above monotherapy'.
- 3.1.3 The most frequent adverse drug reactions reported during efalizumab therapy are mild to moderate dose-related acute flu-like symptoms (associated with the first few doses), leucocytosis and lymphocytosis. Owing to the risk of thrombocytopenia, monthly platelet counts are recommended on initiation of therapy, but the frequency can be decreased to every 3 months with continued treatment. For full details of side effects and contraindications, see the SPC.
- 3.1.4 Efalizumab is administered at an initial single dose of 0.7 mg/kg body weight followed by weekly subcutaneous injections of 1.0 mg/kg body weight (maximum single dose should not exceed a total of 200 mg). The SPC states that the duration of therapy is 12 weeks and may only be continued in patients who respond to treatment. The net price for a 125-mg vial is £169.20 (excluding VAT; 'British national formulary', 49th edition). Costs may vary in different settings because of negotiated procurement discounts.

## **3.2 Etanercept**

- 3.2.1 Etanercept (Wyeth Pharmaceuticals) is a recombinant human tumour necrosis factor (TNF) receptor fusion protein that inhibits the activity of TNF. TNF is a cytokine that is released from T lymphocytes; it mediates inflammation and modulates the cellular immune response. Etanercept is licensed for the 'treatment of adults with moderate to severe plaque psoriasis who have failed to respond to, or who have a contraindication to, or who are intolerant to other systemic therapies including ciclosporin,

methotrexate or PUVA'. It is also licensed for the treatment of active and progressive PsA in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

- 3.2.2 The SPC specifies that etanercept treatment should be initiated and supervised by specialist physicians with experience in the diagnosis and treatment of psoriasis. The SPC also states that the use of etanercept in combination with other systemic therapies or phototherapies has not been studied.
- 3.2.3 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 that may be related to the immunomodulatory activity. There are no monitoring requirements. For full details of side effects and contraindications, see the SPC.
- 3.2.4 Etanercept is administered by subcutaneous injection at a dose of 25 mg twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. The SPC states that treatment with etanercept should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with etanercept is indicated, the above guidance on treatment duration should be followed. 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.

## **4 Evidence and interpretation**

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

## 4.1 *Clinical effectiveness*

### 4.1.1 **Efalizumab**

- 4.1.1.1 A total of five randomised controlled trials (RCTs) that studied efalizumab at a dose of 1 mg/kg once a week were included in the Assessment Report. Across all doses, a total of 3130 participants were randomised. Each trial was placebo-controlled and of 12 weeks duration. Inadequacies in the reporting of the trials meant that the quality of four of the trials could not be properly assessed by the Assessment Group. Outcomes collected included the proportion of patients achieving PASI 50, PASI 75 and PASI 90; PASI score; DLQI score; physician global assessments; itching score; and PsA frequency and severity.
- 4.1.1.2 Not all of the data for each outcome were available. All five trials reported a statistically significant benefit of efalizumab over placebo in the numbers of participants achieving a PASI 50 (pooled relative risk [RR] 3.9, 95% confidence interval [CI] 3.3 to 4.6). Four of the trials reported a PASI 75, and these results were also statistically significant in favour of efalizumab for each trial (pooled RR 7.4, 95% CI 5.2 to 10.7). The one trial reporting a PASI 90 found no statistically significant differences between efalizumab and placebo (RR 5.3, 95% CI 0.9 to 31.7). Only one trial reported mean change from baseline in PASI score; it was 52% for efalizumab-treated patients compared with 19% for placebo-treated patients ( $p < 0.001$ ). DLQI outcomes were reported in four trials, all of which reported a statistically significant greater reduction in patients taking efalizumab; the data could not be pooled due to lack of measures of variance.
- 4.1.1.3 The submission from the manufacturer presented a subgroup analysis of trial IMP24011 ( $n = 793$ ), which included 526 participants who were deemed 'high-need' because they were resistant to, intolerant of or had contraindications to, at least two currently available systemic agents. The numbers achieving a PASI 75 in the whole population were 166/529 (31%) receiving efalizumab and 11/264 (4%) receiving placebo (RR 7.5, 95% CI



4.2 to 13.6). In the 'high-need' subgroup of individuals, 103/342 (30%) of participants who received efalizumab achieved a PASI 75 compared with 6/184 (3%) who received placebo (RR 10.9, 95% CI 4.6 to 26.2). The manufacturer concluded that the efficacy of efalizumab in the high-need group was similar to its efficacy across all treated patients.

- 4.1.1.4 There were no RCTs that had a duration of longer than 12 weeks, although two of the RCTs had 24 week response data from extension periods. Fifteen-month response data were available from an ongoing uncontrolled study, which indicated that response was maintained in patients who continued treatment.
- 4.1.1.5 Pooled data from the five RCTs indicated that there were no statistically significant differences between the efalizumab 1 mg/kg and placebo groups in the number of patients experiencing one or more adverse events, those that had a serious event and those that withdrew due to adverse events. Efalizumab was only licensed in late 2004 and therefore limited data were available relating to long-term adverse events. The SPC states that the safety of efalizumab has not been tested beyond 12 weeks, but the Assessment Group identified data from two 24-week periods, and in one study 339 participants were entered into a 3-year open-label follow-up.

#### **4.1.2 Etanercept**

- 4.1.2.1 The Assessment Report included three double-blind RCTs that evaluated etanercept at a dose of 25 mg or 50 mg twice a week. In total, 1347 patients were enrolled in the RCTs. The Assessment Group deemed all three of the RCTs to be of 'good' quality. At the end of each trial there was an open-label and/or non-randomised extension period.
- 4.1.2.2 All three trials reported statistically significant differences in favour of etanercept 25 mg over placebo as measured by PASI 50, PASI 75 and PASI 90 at 12 weeks. There was no statistically significant heterogeneity

in these results and therefore the results of the trials were pooled. The pooled relative risks were PASI 50 RR 5.41 (95% CI 4.10 to 7.14), PASI 75 RR 10.69 (95% CI 6.15 to 18.57) and PASI 90 RR 18.55 (95% CI 5.24 to 65.69). The trial that continued to 24 weeks also showed a statistically significant difference in favour of etanercept for PASI outcomes. Etanercept 50 mg twice a week also showed statistically significant benefits over placebo in both of the RCTs. The pooled relative risks were PASI 50 RR 6.48 (95% CI 4.84 to 8.66), PASI 75 RR 14.80 (95% CI 8.40 to 26.06) and PASI 90 RR 38.12 (95% CI 9.43 to 154.06). The number of participants who were rated by the physician as being 'clear or almost clear' of psoriasis showed a statistically significant superiority of etanercept at both doses and time-points. The percentage change in PASI and DLQI echoed this, but data were highly skewed and therefore not pooled. At the end of treatment in all three trials there were statistically significant differences in favour of etanercept in the patient measures of disease status.

- 4.1.2.3 In one of the RCTs, patients on etanercept continued taking the drug after the 12-week placebo-controlled period for a further 24 weeks (total treatment period of 36 weeks). The Assessment Group concluded that the results at 36 weeks did not indicate any lessening of response over time.
- 4.1.2.4 The manufacturer also provided the results of the follow-up after discontinuation for two of the RCTs. Although insufficient data were presented for the smaller trial (only 18% of patients were followed), 3-month post-treatment follow-up data were presented for 409 patients who had responded to etanercept treatment in the larger study. Only one of these 409 participants experienced a rebound of their psoriasis to more than 125% of their baseline PASI score. The larger RCT also provided data on patients who were re-treated. Across all doses, the mean difference in PASI score after 12 weeks re-treatment compared with the initial 12-week treatment was -0.5 (95% CI -1.09 to 0.09), indicating that there was no statistically significant difference.

- 4.1.2.5 Post hoc analyses of one of the RCTs examined the efficacy of etanercept in patients who had received prior systemic therapy or phototherapy for psoriasis (89% of patients). Of the 521 patients who had received prior systemic therapy or phototherapy, 337 (65%) had failed to respond to at least one of these treatments. The proportion of patients achieving PASI 75 at week 12 in the etanercept 25 mg twice weekly group was 28% (18/64) in patients whose psoriasis had not failed to respond to prior therapy and 37% (41/112) in patients whose psoriasis had failed to respond to prior therapy. These data have only been published in abstract form, although for licensing purposes, the manufacturer supplied subgroup analyses by prior systemic therapy for all three studies. The EMEA scientific discussion indicated that there was no significant difference in PASI 75 response between patients who had received previous systemic therapy and those who had not.
- 4.1.2.6 The Assessment Group concluded that, in general, etanercept appeared to be well tolerated during short-term and longer-term use. Injection site reaction was the most common adverse event. Across the three trials, a total of 232/415 (56%) people on etanercept 25 mg experienced one or more adverse events compared with 211/414 (51%) people taking placebo (RR 1.10, 95% CI 0.97 to 1.25). The numbers of participants classed as having a serious adverse event were 6/415 (1%) and 4/414 (1%) for the etanercept and placebo groups, respectively (RR 1.50, 95%CI, 0.43 to 5.26). In the two groups, a total of 9/415 (2%) and 10/414 (2%) withdrew because of adverse events (RR 0.90, 95% CI 0.97 to 2.19). There were no statistically significant differences in adverse event rates between the patients taking etanercept 50 mg and those taking placebo.
- 4.1.2.7 The Assessment Group undertook a formal evidence synthesis with the aim of bringing together the clinical evidence regarding the efficacy of etanercept, efalizumab and other treatments. This evidence synthesis generated parameter estimates (response rates) used in the economic modelling. The evidence synthesis found that efalizumab was less

effective than etanercept 25 mg, and both were less effective than infliximab, methotrexate and ciclosporin. The 50 mg dose of etanercept was found to be more effective than the 25 mg dose.

## **4.2 Cost effectiveness**

### **4.2.1 Published economic evaluations**

4.2.1.1 The Assessment Group did not identify any published economic evaluations that considered efalizumab. The Assessment Group identified only one published economic evaluation of etanercept that met its inclusion criteria. The base-case analysis found UVB phototherapy to be the most cost-effective option, followed by methotrexate. Of the three biological therapies examined (infliximab, etanercept and alefacept), infliximab was found to be the most cost effective, although it was still less cost effective than non-biological treatments. The analysis, however, had limited usefulness for decision making primarily because it was US-based and the results were not expressed as incremental costs per quality-adjusted life year (QALY).

### **4.2.2 Efalizumab – manufacturer’s model**

4.2.2.1 The manufacturer developed a decision-tree-based model, which compared the cost effectiveness of efalizumab treatment with that of topical therapies (based on calcipotriol and betamethasone) over a 10-year timeframe. Utilities (based on a time trade-off approach) were obtained from a study of 87 people with psoriasis. In order to estimate QALYs, the number of successfully treated years was multiplied by the difference in utility between a PASI 50 responder and a non-responder. There were no published PASI 50 response rates for topical therapies in people with moderate to severe psoriasis; therefore the rates associated with the placebo arms of the efalizumab RCTs (which permitted concomitant topical therapy use) were used. With the exception of a small proportion of patients who discontinue therapy for reasons unrelated to

efficacy or adverse events, it was assumed that patients responding at 12 weeks (in terms of PASI 50) would continue to respond for a further 10 years. Resource use due to adverse events was included in the model.

- 4.2.2.2 In the base-case scenario, costs were discounted by 6% and outcomes were discounted by 1.5%. Over the 10-year time horizon, expected 'quality-adjusted response years' with efalizumab were estimated to be 1.39 versus 0.36 for a treatment strategy beginning with topical therapy. The incremental cost/QALY results from the deterministic and probabilistic analyses were around £25,600 and £25,800, respectively. The data were subject to a number of deterministic sensitivity analyses; the incremental cost-effectiveness ratio (ICER) remained below £30,000 under most scenarios.

#### **4.2.3 Etanercept – manufacturer's model**

- 4.2.3.1 The manufacturer of etanercept developed a Markov model using pooled data from the three registration RCTs. It aimed to assess the cost effectiveness of etanercept 25 mg (twice weekly), etanercept 50 mg (twice weekly) and an option of topical therapy only. A mapping exercise was used to estimate the relationship between DLQI (measured in the trials) and utility. Average improvement in utility was multiplied by the time between visits to estimate QALY gain between the visits. The manufacturer modelled a 12-week time horizon and longer-term outcomes (comprising eight 12-week treatment periods) by means of extrapolation. No discounting on costs and effects appears to have been applied and adverse events were not explicitly included.
- 4.2.3.2 The short-term (12-week) analysis estimated that the ICER for etanercept 25 mg over no systemic therapy was almost £125,000; the ICER for etanercept 50 mg was substantially higher. In the longer-term (96-week) analysis, the ICER for intermittent 25 mg etanercept treatment versus placebo was estimated to be £37,200. When people with relatively severe psoriasis (PASI greater than 10) and a poor quality of life (DLQI greater

than 15) at baseline were considered in the 96-week analysis, the ICERs for etanercept versus systemic therapy declined markedly. For intermittent 25 mg etanercept therapy, the ICER in this subgroup was found to be around £24,000 per QALY, respectively.

#### **4.2.4 The Assessment Group model**

- 4.2.4.1 The Assessment Group developed its own model for assessing the cost effectiveness of efalizumab and etanercept. The main analysis compared efalizumab (continuous), etanercept (intermittent 25 mg and 50 mg, and continuous 25 mg) and supportive care without DMARDs or biological therapies. Utilities were estimated by mapping the mean change in DLQI score (conditional on PASI response) to changes in EQ-5D (a non-disease specific instrument for describing and valuing HRQoL). When modelling intermittent etanercept treatment, it was assumed that the time between 12 week treatment cycles would be 29 days, resulting in 3.2 treatment cycles per year. This was based on the median duration of PASI 75 response as reported in an unpublished etanercept re-treatment study. Annual discount rates of 6% on costs and 1.5% on outcomes were applied in the analyses. Adverse events were not directly modelled. Decision uncertainty was examined using probabilistic sensitivity analysis.
- 4.2.4.2 The base-case analysis showed that supportive care is the only cost-effective strategy until the threshold reaches £70,000 per QALY. The ICER for intermittent low-dose (25 mg) etanercept was found to be £65,320 per QALY gained. The ICER for intermittent high-dose (50 mg) etanercept treatment was substantially higher. Efalizumab was dominated in the analysis by intermittent etanercept 25 mg. The results of several alternative scenarios presented indicated that the cost effectiveness of efalizumab and etanercept varied considerably according to baseline DLQI and whether it was assumed that all non-responders were hospitalised for 21 days annually. In all cases, the ICERs of the biological agents were found to be lower than in the base case; but efalizumab was less cost-

effective than intermittent etanercept 25 mg. In the scenario that considered both poor baseline quality of life and hospitalisation for non-responders, the ICER for intermittent etanercept 25 mg was £14,460 per QALY gained.

### **4.3 Consideration of the evidence**

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of etanercept and efalizumab, having considered evidence on the nature of the condition and the value placed on the benefits of etanercept and efalizumab by people with psoriasis, those who represent them, and clinical experts. It was also mindful of the need take account of the effective use of NHS resources.
- 4.3.2 The Committee accepted that the RCTs demonstrated the clinical effectiveness of etanercept and efalizumab in people with moderate to severe plaque psoriasis. The Committee noted that the inclusion criteria for the RCTs did not wholly reflect the population for which these technologies are currently licensed because their psoriasis had not necessarily failed to respond to other treatment options. The Committee noted, however, that one of the efalizumab trials did include a subgroup of patients whose psoriasis had failed to respond to previous therapy and that post hoc analyses of one of the etanercept trials examined the effectiveness of this technology in people whose condition had failed to respond to at least one prior systemic therapy. The Committee also heard from the clinical experts that, in clinical practice, these drugs were used according to the licensed indications and were as effective for people who had not responded to other available treatments as for those who were treatment naïve. The Committee considered, therefore, that the overall baseline characteristics of the patients included in the trials indicated that they were a population with relatively severe psoriasis.
- 4.3.3 The Committee considered carefully the clinical effectiveness of etanercept and efalizumab on the basis of dose administered and duration of therapy

within their respective licensed indications. It noted that according to the SPCs the maximum duration of etanercept therapy within any one cycle of treatment is 24 weeks and that treatment should be stopped in non-responders at 12 weeks. However, no stipulations are made in the SPC as to the period needed to be allowed between successive treatment cycles. The experts advised the Committee that people who had responded to etanercept sometimes relapsed within weeks of stopping therapy and therefore in some people the interval between successive cycles could be short. The experts also indicated that in their clinical experience 12 weeks was a sufficient period of time in which to determine whether a patient was likely to respond to treatment with either etanercept or efalizumab. This experience was in accordance with the recent British Association of Dermatologists guidelines. The experts also advised that people who responded at this stage would be suitable for either further cycles of etanercept or continuous therapy with efalizumab.

4.3.4 In considering the economic modelling the Committee recognised that there was considerable uncertainty in the estimates of cost effectiveness that had been produced. This uncertainty related principally to estimates of the efficacy of the alternative interventions and treatment regimens and the evidence on long-term outcomes. In addition, the Committee noted the differences in modelling approaches adopted by the manufacturers and the Assessment Group, and their respective weaknesses and strengths.

4.3.5 Noting this uncertainty in the economic modelling, the Committee concluded it was unlikely that these interventions would be cost effective except in people who had very poor quality of life and who would be likely to require hospital admission for treatment. Testimony from the clinical experts and consultees suggested that these people would be those with severe disease as defined by a PASI of ten or more and DLQI of more than ten, who had not responded to standard systemic therapies. The Committee noted that the SPCs for etanercept and efalizumab state that the interventions are indicated in adults who have failed to respond to, who have a



contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate and/or PUVA.

- 4.3.6 The Committee noted that in all cost-effectiveness scenarios of the Assessment Group model efalizumab was dominated by intermittent 12-weekly cycles of etanercept 25 mg (that is, efalizumab treatment was more costly and slightly less effective). The Committee noted that there were data supporting the continued efficacy of etanercept when administered on an intermittent basis according to its licensed indications. In particular it noted that in the re-treatment study discussed in 4.1.2.4 there was no statistically significant difference in mean absolute PASI score after 12 weeks of re-treatment compared with the initial 12 weeks of treatment. In addition, the Committee was also aware that the Assessment Group model took into account data from the manufacturers relating to a median duration of PASI 75 response of 29 days as reported in an unpublished etanercept re-treatment study. On this basis the Committee was persuaded that intermittent treatment with etanercept would be clinically effective in a population of adults with psoriasis, and also more cost effective than treatment with continuous efalizumab, principally because of the treatment-free periods that characterise intermittent therapy.
- 4.3.7 The Committee did, however, consider that because the two drugs had different mechanisms of action, it was possible that people whose psoriasis had not responded to etanercept might well have a response to efalizumab. Given that other treatment options available for these people were limited, the Committee concluded that efalizumab should be recommended for use in the group of people whose psoriasis had failed to respond to etanercept (using the response criteria in Section 1.2) or who were either intolerant of or had definite contraindications to etanercept. The Committee was also persuaded that patients who have been shown to experience severe relapse early after discontinuation of etanercept therapy might not be suitable for intermittent treatment. Under these circumstances the choice between rapid reinstatement of intermittent etanercept and changing to continuous

efalizumab should be made on clinical grounds as either approach was likely to be equally cost effective.

4.3.8 The Committee additionally considered the cost effectiveness of the use of the 50-mg twice-weekly dose of etanercept in the subgroup of people who had very poor quality of life. It was aware that within the SPC, the 50-mg dose is allowable only for a period of 12 weeks for etanercept-naïve patients and should not be used for repeat cycles of therapy in patients who respond initially and then subsequently relapse. The experts commented that the 50-mg dose may be of use in patients who had particularly severe psoriasis in order to achieve more rapid control of their symptoms. The Committee was not persuaded that this very severe subgroup had been sufficiently defined (in terms of PASI score or DLQI at baseline) or that their potential for an enhanced response was supported by trial data. There was also no evidence that an initial 12-week period of 50 mg achieved better longer-term outcomes than an initial 25 mg dose. The Committee noted that the Assessment Group's economic model had shown that the (unlicensed) use of the intermittent 50 mg twice-weekly regimen of etanercept was not cost effective. The Committee were aware that the licensed scenario of an initial 12 weeks treatment with 50 mg etanercept twice weekly in etanercept naïve patients had not been directly modelled. However, the Committee was persuaded that the economic modelling had shown that the use of the higher dose of etanercept for 12 weeks was not a cost-effective option compared with the intermittent use of 25 mg twice weekly: the increased drug acquisition cost would substantially outweigh the benefits obtained from an initial 12 weeks at a higher dose. The Committee therefore concluded that etanercept should not be recommended at doses exceeding 25 mg twice weekly.

4.3.9 The Committee considered the most appropriate criteria for assessment of response to treatment. It was aware that the EMEA recognises that reduction of baseline PASI score by 75% (PASI 75) is an indicator that severe psoriasis has responded to treatment. Additionally the British Society

for Rheumatology guidelines on the use of these agents in PsA also recommends collecting PASI data at baseline and using the PASI 75 as an indicator of response. Therefore, the Committee considered that a criterion for adequacy of response for both drugs assessed at 12 weeks should be the PASI 75. It was however persuaded that the evidence and the expert testimony indicated that there were a number of individuals who, on the basis of assessment of improvement in quality of life, would derive significant benefit from etanercept or efalizumab, but might have failed to achieve a PASI 75 after 12 weeks of treatment. The Committee therefore considered that the assessment of response should also include a measure of quality of life improvement as defined by a change from the baseline DLQI at initiation of treatment. It concluded that it would also be appropriate for individuals to continue on treatment if they had achieved a PASI 50 response providing they had also achieved a five-point reduction in their DLQI score from when treatment was initiated. This view was supported by recent guidelines from the British Association of Dermatologists on the use of biological interventions in psoriasis. The Committee also concluded that if people had failed to reach these response criteria at 12 weeks then treatment should be discontinued. It further concluded that re-treatment in these patients would not be appropriate as there was no evidence to suggest that the response would differ in subsequent cycles.

- 4.3.10 The Committee considered the possibility of adverse events with etanercept and efalizumab both in the short and longer term; it noted that there was currently little information on the use of these drugs in people with psoriasis beyond the duration of the RCTs. It was also aware that these drugs could increase risk of malignancy and that people with psoriasis were potentially already at an increased risk of skin cancer as a result of therapeutic exposure to ultraviolet radiation. Additionally the possibility of recrudescence of latent tuberculosis has been associated with the use of etanercept. Consequently the Committee agreed with the experts' advice that a register should be established in order to collect information on long-term outcomes

(including adverse effects) in patients with psoriasis treated with cytokine inhibitors. The Committee therefore strongly supported the rapid establishment of the proposed British Association of Dermatologists Biological Interventions Register (BADBIR). It also considered that, in order to ensure that all relevant data were captured, procedures should be implemented to allow cross-referencing of BADBIR with information from people with PsA enrolled in the British Society for Rheumatology biologics register.

- 4.3.11 The Committee also discussed who should initiate treatment and monitor the use of etanercept and efalizumab in patients with psoriasis. The Committee took note of the content of the SPC for each drug. In addition, it heard evidence from experts who strongly argued that treatment strategies should take into account the fact that certain people will have concomitant PsA. The Committee therefore agreed that the use of etanercept and efalizumab should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. Furthermore, if a person has concomitant psoriasis and PsA their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

## **5 Recommendations for further research**

- 5.1.1 The Committee noted that there are a number of ongoing studies of etanercept and efalizumab in people with psoriasis. However, it stressed that efficacy trials conducted in the specific population for which etanercept and efalizumab are licensed are required – that is, people with moderate to severe disease in whom conventional therapy has failed or is inappropriate. In addition, these trials should be of adequate duration and compare etanercept and efalizumab with each other and with other treatments for moderate to severe plaque psoriasis. Information should also be collected on the use of these drugs in combination with other therapies.

- 5.1.2 Efforts should be made to ensure the rapid establishment of the proposed BADBIR. This will enable the collection of information on long-term outcomes including adverse events, and also potentially facilitate the identification of subgroups of people who respond better to the drugs. Procedures should be implemented to allow cross-referencing of BADBIR with information from people with PsA enrolled in the British Society for Rheumatology biologics register.
- 5.1.3 Research on the rate of inpatient hospitalisation in people with moderate to severe psoriasis is warranted, and the effect of treatment on this rate.
- 5.1.4 Research on the utility of different health states and how these relate to existing measurement scales is needed in dermatology.

## **6 Implementation**

- 6.1 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.
- 6.2 '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.

- 6.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website ([www.nice.org.uk/TAXXX](http://www.nice.org.uk/TAXXX)).

*[Note: tools will be available when the final guidance is issued]*

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

## 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](http://www.nice.org.uk)).

- Etanercept and infliximab for the treatment of PsA (ongoing appraisal).

## 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 these technologies will be considered for review after 2 years.

- 8.3 David Barnett  
Chair, Appraisal Committee  
August, 2005

## **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 Dr Nerys Woolcott, Dr Neil Hawkins, Mrs Anne Mason, Ms Anita Kainth, Ms Zarnie Khadjesari, Ms Yolanda Bravo Vergel, Ms Kate Misso, Ms Kate Light, Dr Robert Chalmers, Professor Mark Sculpher, and Dr Rob Riemsma, Centre for Reviews and Dissemination, University of York, York, *Efalizumab and Etanercept for the Treatment of Psoriasis*, 4 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, 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
  - Serono Pharmaceuticals 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
  - Psoriasis Association
  - Psoriasis Arthropathy alliance
  - Royal College of Nursing
  - Royal College of Paediatrics and Child Health
  - Royal College of Physicians

- Royal Pharmaceutical Society of Great Britain
- Skin Care Campaign

III Commentator organisations (without the right of appeal):

- British National Formulary
- National Public Health Service for Wales
- NHS Quality Improvement Scotland
- Centre of Evidence-based Dermatology, University of Nottingham
- 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 efalizumab for the treatment of adults with psoriasis by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD:

- Professor Jonathon Barker, Professor of Dermatology, University of Manchester
- Professor Christopher Griffiths, Professor of Dermatology, University of Manchester
- Mr Richard Groves, Head of Clinical Immunodermatology, St. Johns Institute of Dermatology
- 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 efalizumab and etanercept for the treatment of adults with psoriasis**

### ***Possible objectives for an audit***

An audit could be carried out to ensure that efalizumab and etanercept are used appropriately in the treatment of adults with plaque psoriasis.

### ***Possible patients to be included in the audit***

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

An alternative could be to find patients for whom efalizumab or etanercept has been prescribed as treatment for plaque psoriasis, 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 efalizumab and etanercept for the treatment of plaque psoriasis are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. An adult with plaque psoriasis is prescribed etanercept, within its licensed indications, at a dose not exceeding 25 mg twice weekly only when <b>both</b> of the following criteria are met</p> <p>a. The disease is severe <b>and</b></p> <p>b. The psoriasis has failed to respond to standard systemic therapies, or the person is intolerant to, or has a contraindication to, these treatments</p>	<p>100% of adults who are prescribed etanercept for plaque psoriasis</p>	<p>None</p>	<p>'Severe' psoriasis means a total Psoriasis Area Severity Index (PASI) <math>\geq 10</math> <b>and</b> a Dermatology Life Quality Index (DLQI) <math>&gt; 10</math>.</p> <p>Clinicians will need to agree locally on how to define 'failed to respond to' and 'intolerance to' standard systemic therapies, for audit purposes.</p> <p>'Standard systemic therapies' include ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation).</p> <p>(As a guide for designing the audit, see the British Association of Dermatologists Guidelines for use of biological interventions in psoriasis for more detail related to definitions.)</p> <p>See the summaries of product characteristics for contraindications to standard systemic therapies in routine use</p>
<p>2. A person with plaque psoriasis is prescribed efalizumab, within its licensed indications, only when <b>all</b> of the following criteria are met</p>	<p>100% of adults who are prescribed efalizumab for plaque psoriasis</p>	<p>A person had begun a course of treatment with efalizumab at the date of publication of this guidance and has opted to continue to receive treatment until the person and his or</p>	<p>'Responded to treatment with etanercept' is defined as a 75% reduction in the PASI score from when treatment started (PASI 75) <b>or</b> a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in</p>

<p>a. The disease is severe <b>and</b>  b. The psoriasis has failed to respond to standard systemic therapies or the person is intolerant to, or has a contraindication to, these treatments <b>and</b>  c. The psoriasis has failed to respond to etanercept or the person is intolerant to, or has a contraindication to etanercept</p>		<p>her clinicians consider it is appropriate to stop</p>	<p>DLQI 12 weeks from when treatment started.  See the SPC for contraindications to etanercept.  Clinicians will need to agree locally on how to document the patient's option of continuing to receive efalizumab until it is considered appropriate to stop</p>
<p>3. The response to etanercept or efalizumab is assessed at 12 weeks of treatment using the PASI and DLQI</p>	<p>100% of the people for whom etanercept or efalizumab has been prescribed for severe psoriasis and who have been on the drug for at least 12 weeks</p>	<p>None</p>	<p>Assessment is to determine the response to treatment for either etanercept or efalizumab. See above for the definition of response to treatment. Clinicians will need to agree locally to how assessment of response to treatment is documented, for audit purposes</p>
<p>4. The prescription of etanercept or efalizumab is discontinued at 12 weeks unless the psoriasis has responded adequately to treatment</p>	<p>100% of the people for whom etanercept or efalizumab has been prescribed for severe psoriasis and who have been on the drug for at least 12 weeks</p>	<p>None</p>	<p>See above for relevant definitions</p>
<p>5. Further treatment is</p>	<p>0% of people for whom</p>	<p>None</p>	<p>See above for relevant definitions</p>

prescribed for people whose psoriasis does not adequately respond at 12 weeks	etanercept or efalizumab has been prescribed and whose psoriasis has not responded adequately		
6. The use of etanercept and efalizumab for psoriasis is initiated and supervised only by a specialist physician experienced in the diagnosis and treatment of psoriasis	100% of the people for whom etanercept or efalizumab has been prescribed for severe psoriasis	If a person has both psoriasis and psoriatic arthritis, 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 and efalizumab for psoriasis 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.

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

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.