NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Ustekinumab for the treatment of adults with moderate to severe psoriasis

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met.

- The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more **and** a Dermatology Life Quality Index (DLQI) score of more than 10.
- The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments.
- The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial.

1.2 Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either:

- a 75% reduction in the PASI score (PASI 75) from when treatment started **or**
- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started.

1.3 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.

2 The technology

2.1 Ustekinumab (Stelara, Janssen-Cilag) is a fully human monoclonal antibody that targets interleukin-12 (IL-12) and IL-23. It binds to the p40 subunit, common to both IL-12 and IL-23, which prevents these cytokines from binding to the cell surface of T cells, thereby disrupting the inflammatory cascade implicated in psoriasis. Ustekinumab has a UK marketing authorisation for 'the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA'. The recommended dose of ustekinumab is 45 mg for people who weigh 100 kg or less, and 90 mg for people who weigh over 100 kg. An initial dose of ustekinumab is administered subcutaneously at week 0, followed by another dose at week 4, and then a further dose every 12 weeks. The summary of product characteristics (SPC) states that ustekinumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

2.2 Common adverse events associated with ustekinumab, as reported in the SPC, include upper respiratory tract infection, nasopharyngitis, depression, headache, dizziness, diarrhoea, pruritus, back pain, fatigue and injection site erythema. Contraindications listed in the SPC include clinically important active infection and hypersensitivity to the active substance or to any of the excipients. For full details of side effects and contraindications, see the SPC.

2.3 Ustekinumab is available in vials containing 45 mg. The cost per vial is £2147 (Monthly Index of Medical Specialities [MIMS], April 2009). Ustekinumab is not listed in the current version of the 'British national formulary' (BNF; edition 57). The cost of ustekinumab for the two loading doses (at 0 and 4 weeks) is £4294. The cost in the first year is £10,735, with an annual cost thereafter of £9335 (the annual cost assumes an average of 4.3 injections per year). Costs may vary in different settings because of negotiated procurement discounts.

2.4 The SPC recommends that people whose body weight exceeds 100 kg should receive a dose of 90 mg of ustekinumab. This would be double the cost of the 45 mg dose indicated for the treatment of a person who weighs 100 kg or less. However, the manufacturer has proposed a patient access scheme to the Department of Health. Under the scheme, for people who weigh more than 100 kg and who are prescribed the 90 mg dose (two 45 mg vials), the manufacturer will provide both vials at a total cost of £2147 (the cost of a single vial). The manufacturer has proposed that this patient access scheme will be available to the NHS at least until either a review of the guidance by NICE or the introduction of any new formulations that would render the scheme obsolete. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of ustekinumab and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The decision problem in the manufacturer's submission compared ustekinumab with adalimumab, efalizumab, etanercept, infliximab and supportive care. Three doses of etanercept were considered: 25 mg twice weekly given intermittently as recommended in 'Etanercept and efalizumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 103 [TA103]), 25 mg twice weekly given continuously, and 50 mg twice weekly given for the first 12 weeks followed by a reduction in dose to 25 mg twice weekly. Clinical outcomes in the manufacturer's submission included improvements in PASI and DLQI scores. PASI is a measure of disease severity based on body surface area affected and the extent, scaliness, thickness and redness of plaques, with scores ranging from 0 to 72. The DLQI is a disease-specific quality-of-life measure with scores ranging from 0 to 30. Moderate to severe psoriasis was defined as a PASI score of 10 or more and a DLQI score of more than 10.

3.2 The manufacturer's submission included evidence from three randomised controlled trials (RCTs):

- PHOENIX-1 (n = 766, 5 years' duration), a phase III, multicentre, parallel, randomised, double-blind, placebo-controlled trial based in the USA, Canada and Belgium.
- PHOENIX-2 (n = 1230, 5 years' duration), a phase III, multicentre, parallel, randomised, double-blind, placebo-controlled trial based in Europe and North America.
- ACCEPT trial (n = 903, 64 weeks' duration), a phase III, multicentre, parallel RCT based in Europe and North America, which compared ustekinumab with etanercept (50 mg twice weekly for the first 12 weeks).

3.3 In each of the RCTs, two doses (45 mg and 90 mg) of ustekinumab were investigated and patients were randomised to groups

regardless of their body weight. To reflect the licensed dosing of ustekinumab, the manufacturer presented two analyses in their submission. The first analysis used data from all the patients enrolled in the clinical trials and included dosing outside the marketing authorisation (that is, patients weighing 100 kg or less who received ustekinumab 90 mg and patients weighing over 100 kg who received ustekinumab 45 mg). The second was a subgroup analysis that included data only for patients who received ustekinumab according to the marketing authorisation (weight-based dosing; that is, 45 mg for people weighing 100 kg or less and 90 mg for people weighing over 100 kg).

3.4 The results of the three RCTs using data for all patients demonstrated statistically significant differences in the percentage of patients treated with ustekinumab who achieved a 75% or greater reduction in PASI score (PASI 75; the primary endpoint in the trials) compared with those who received placebo. The percentages of patients with at least a PASI 75 response at week 12 in the ustekinumab 45 mg, ustekinumab 90 mg and placebo groups were 67%, 66% and 3% respectively in the PHOENIX-1 trial ($p < 0.001$ for both ustekinumab doses compared with placebo) and 67%, 76% and 4% respectively in the PHOENIX-2 trial ($p < 0.001$). In the ACCEPT trial, the percentages of patients with at least a PASI 75 response at week 12 in the ustekinumab 45 mg, ustekinumab 90 mg and etanercept groups were 68%, 74% and 57% respectively ($p = 0.012$ for ustekinumab 45 mg and $p < 0.001$ for ustekinumab 90 mg compared with etanercept).

3.5 For secondary outcomes recorded in the RCTs, such as the physician's global assessment (PGA) score, the DLQI score and other health-related quality-of-life scores, the ustekinumab groups showed statistically significant improvements compared with the

placebo groups. In the PHOENIX-1 trial, the mean change in DLQI score at week 12 was −8.0 for ustekinumab 45 mg, −8.7 for ustekinumab 90 mg and −0.6 for placebo ($p < 0.001$ versus placebo for both ustekinumab doses). In the PHOENIX-2 trial, the values were −9.3, −10.0 and −0.5 respectively ($p < 0.001$ versus placebo for both ustekinumab doses). DLQI data were not collected in the ACCEPT trial.

3.6 Data from the clinical trials suggested that 90 mg is a more effective dose of ustekinumab than 45 mg for patients who weigh more than 100 kg. For example, in the PHOENIX-1 trial, 69% of patients weighing more than 100 kg who received ustekinumab 90 mg achieved a PASI 75 response at 12 weeks, compared with 54% of those who received ustekinumab 45 mg. In the PHOENIX-2 trial, the values were 71% and 49% respectively.

3.7 The manufacturer included longer-term data from the PHOENIX trials for the weight-based dosing subgroup analysis. These data suggested that the PASI response rates observed during the double-blind, randomised phases of the studies were maintained in the longer term. In the PHOENIX-1 trial, the percentages of patients achieving a PASI 75 response at week 24 were 83% and 80% for ustekinumab 45 mg and 90 mg respectively. In the PHOENIX-2 trial, the respective percentages were each 80%.

3.8 In the PHOENIX-1 trial, the percentages of patients having one or more adverse events were 57.3%, 51.4% and 47.8% in the ustekinumab 45 mg, ustekinumab 90 mg and placebo groups respectively. The percentages of patients having a serious adverse event were 0.8%, 1.6% and 0.8% respectively. Similar rates of adverse events were reported in the PHOENIX-2 trial. In the ACCEPT trial, the percentages of patients having one or more adverse events were 66.0%, 68.3% and 69.5% in the ustekinumab

45 mg, ustekinumab 90 mg and etanercept groups respectively. The percentages of patients having a serious adverse event were 1.9%, 1.2% and 1.2% respectively.

3.9 The manufacturer compared ustekinumab with other biological therapies (that is, adalimumab, efalizumab, infliximab and etanercept) using a mixed treatment comparison. This included data from studies that compared different biological therapies directly, as well as indirect comparisons using data from studies that compared biological therapies with placebo using the placebo group as the common factor. The manufacturer included data from the three ustekinumab RCTs, as well as from three RCTs comparing adalimumab with placebo, five comparing efalizumab with placebo, five comparing etanercept with placebo and four comparing infliximab with placebo. The results from the mixed treatment comparison using the ustekinumab data for all patients suggested that the mean probabilities of achieving a PASI 75 response were 69% for ustekinumab 45 mg (95% confidence interval [CI] 62% to 75%), 74% for ustekinumab 90 mg (95% CI 68% to 80%), 58% for adalimumab (95% CI 49% to 68%), 80% for infliximab (95% CI 70% to 87%), 39% for etanercept 25 mg (95% CI 30% to 48%), 52% for etanercept 50 mg (95% CI 45% to 59%), 26% for efalizumab (95% CI 21% to 32%) and 4% for supportive care (95% CI 3% to 4%). The manufacturer also included a mixed treatment comparison for the weight-based dosing subgroup analysis. However, the ustekinumab data from this comparison were provided as academic in confidence.

3.10 The manufacturer based its cost-effectiveness analysis on the economic model used in TA103 and subsequently in 'Infliximab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 134 [TA134]) and 'Adalimumab for the treatment of adults

with psoriasis' (NICE technology appraisal guidance 146 [TA146]). The model was adapted by the manufacturer of ustekinumab to incorporate additional evidence, including the results of the mixed treatment comparison described in section 3.9.

3.11 In the model, each person had an initial period of treatment after which response was assessed (this was referred to as the trial period). Continuation of treatment into the next phase (referred to as the treatment period) occurred only if a PASI 75 response was achieved in the trial period. The time at which the response was assessed varied for the different drugs, depending on their dosing regimen. The assessment points were at 12 weeks (etanercept), 10 weeks (infliximab) and 16 weeks (adalimumab and ustekinumab). It was assumed that for people whose psoriasis responded to treatment, 20% stopped treatment each subsequent year. The mean time on treatment using this assumption was calculated to be 3.65 years. The same assumption was used for all biological therapies.

3.12 The utility data used in the model were based on an estimate of the relationship between PASI response rates and changes in DLQI score from the PHOENIX-1 and PHOENIX-2 trials mapped to EQ-5D scores. First, the mean change in the DLQI score between baseline and week 12 was estimated for groups of patients with different levels of PASI response. Secondly, the manufacturer estimated an algorithm to map DLQI scores to EQ-5D scores from a scatter plot published in the assessment report of TA103. The changes in mean EQ-5D score for PASI responses of less than 50%, between 50% and 74%, between 75% and 89%, and 90% or more were estimated to be 0.04, 0.17, 0.22 and 0.25 respectively.

3.13 The costs in the economic model included drug costs, administration costs and monitoring costs, and were taken from the

model in TA103, NHS Reference Costs, and the BNF (edition 56). The Personal Social Services Research Unit (PSSRU) inflation index was used to update costs from 2006 values if current costs were not available. The model assumed that people whose psoriasis had not responded adequately to treatment would have an inpatient admission of 21 days' duration once a year.

3.14 The manufacturer's base-case analysis assumed a weighted average of weight-based dosing whereby 80% of people received ustekinumab 45 mg and 20% of people received ustekinumab 90 mg. The manufacturer also provided analyses using the data from all patients in the clinical trials and the data from the weight-based dosing approach with separate estimates for ustekinumab 45 mg and 90 mg. All the analyses in the submission assumed that the patient access scheme (see section 2.4) was in place.

3.15 The base-case analysis showed that when ustekinumab was compared with supportive care, the QALY gain was 0.156 at an incremental cost of £4615, giving an incremental cost-effectiveness ratio (ICER) of £29,587 per QALY gained. The ICER for ustekinumab compared with etanercept 25 mg given intermittently (assuming 88% of the cost of continuous etanercept) was £27,105 per QALY gained. The ICER for infliximab compared with ustekinumab was £304,566 per QALY gained. Adalimumab and etanercept given continuously rather than intermittently were dominated by ustekinumab (that is, ustekinumab had both greater effectiveness and lower costs). Probabilistic sensitivity analyses suggested that the probabilities of ustekinumab being cost effective at £20,000 and £30,000 per QALY gained were 7.4% and 48.5% respectively. The manufacturer's analyses suggested that ustekinumab was the only biological therapy that was likely to be cost effective at £20,000 and £30,000 per QALY gained.

3.16 The analyses using data for all patients (that is, no weight-based dosing) presented separate ICERs for ustekinumab 45 mg and 90 mg. These analyses suggested that when ustekinumab 45 mg was compared with supportive care, the QALY gain was 0.1544 at an incremental cost of £4735, giving an ICER of £30,664 per QALY gained. The estimates for ustekinumab 90 mg suggested a QALY gain of 0.1563 and incremental costs of £4613, giving an ICER of £29,520 per QALY gained. The ICERs for ustekinumab in comparison with intermittent etanercept 25 mg were £36,938 per QALY gained for ustekinumab 45 mg and £28,633 per QALY gained for ustekinumab 90 mg. Etanercept 25 mg given continuously was dominated by ustekinumab. Adalimumab was dominated by ustekinumab 90 mg, but for ustekinumab 45 mg the ICER was £16,400 per QALY gained.

3.17 Sensitivity analyses were carried out to test assumptions in the economic model. When the manufacturer reduced the length of an inpatient stay for people whose psoriasis did not respond adequately to treatment from the base-case estimate of 21 days to 17.5 days, the ICER for ustekinumab in comparison with supportive care increased from £29,587 to £34,387 per QALY gained. When the length of stay was increased to 27.5 days, the ICER decreased to £20,672 per QALY gained. The manufacturer also changed the way in which estimates of utility were obtained: from EQ-5D data mapped from DLQI scores, to SF-6D data transformed from SF-36 values collected in the PHOENIX-1 trial. When SF-6D data were used to estimate utilities, the ICER for ustekinumab compared with supportive care increased from £29,302 to £49,371 per QALY gained.

3.18 The manufacturer also varied the assumptions about the cost and efficacy of intermittent etanercept. The cost of intermittent

compared with continuous etanercept was changed from the base-case estimate of 88% to 74% (the figure used in TA103) and to 98%. Using an estimate of 74%, the ICER for ustekinumab compared with intermittent etanercept 25 mg increased from £27,105 to £68,339 per QALY gained. When an estimate of 98% was used, ustekinumab dominated intermittent etanercept. The relative efficacy of intermittent compared with continuous etanercept was assumed to be 81% in the base case. When this estimate was changed to 71%, the ICER for ustekinumab compared with intermittent etanercept decreased to £22,634 per QALY gained. When the estimate was changed to 91%, the ICER was £32,949 per QALY gained.

3.19 The ERG concluded that the manufacturer's submission provided an unbiased estimate of the clinical effectiveness of ustekinumab at 12 weeks based on the results of the three randomised comparisons. However, it noted that there was a lack of information about the methodology used for the weight-based dosing subgroup analysis. In addition, it could not determine whether the methods used were appropriate and whether the subgroup analysis supported the weight-based categorisation presented.

3.20 The ERG commented that there appeared to be differences between the mixed treatment comparison that had been used in the appraisal of etanercept and efalizumab (TA103) and that used in the current appraisal. The ERG also noted that the manufacturer's submission included only minimal discussion of any possible clinical heterogeneity between the trials included in the mixed treatment comparison. It further noted that in the mixed treatment comparison, data from the weight-based dosing analysis of ustekinumab were taken from a subgroup of the trial data, whereas data for all patients were used for the comparator trials. The ERG

was concerned that this had affected randomisation. The ERG concluded that the clinical effectiveness of ustekinumab in comparison with the other biological therapies was uncertain.

3.21 The ERG also noted that the probabilistic sensitivity analysis in the manufacturer's submission appeared to include only variables for utilities, treatment response and the proportion of people weighing more than 100 kg. It did not include other variables to which the ICERs were sensitive, such as the number of hospital days, the effects of different inpatient costs and the relative efficacy of intermittent etanercept.

3.22 The ERG completed an exploratory analysis that amended the base-case analysis to include the price for ustekinumab 90 mg as double the list price of ustekinumab 45 mg (that is, assuming that there would be no patient access scheme in place). The results showed that the ICER for ustekinumab compared with supportive care increased from £29,587 to £40,952 per QALY gained. A further exploratory analysis assumed that the efficacy of intermittent etanercept 25 mg was the same as that of continuous etanercept 25 mg (as was assumed in the economic model for TA103). Using this assumption, the ICER for ustekinumab compared with intermittent etanercept 25 mg in the base-case analysis increased from £27,105 to £41,449 per QALY gained.

3.23 The ERG conducted an exploratory probabilistic sensitivity analysis that included a larger number of variables than were included by the manufacturer. The results of the ERG's analysis suggested greater uncertainty around the estimates of cost effectiveness, but the cost-effectiveness acceptability curves did not differ significantly from those of the manufacturer. When the ERG repeated the analysis assuming that the cost of ustekinumab 90 mg was twice that of ustekinumab 45 mg, the results showed that the probability

of ustekinumab being considered cost effective at £20,000 and £30,000 per QALY gained was zero.

3.24 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ustekinumab, having considered evidence on the nature of plaque psoriasis and the value placed on the benefits of ustekinumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee discussed the likely place of ustekinumab in the management of severe plaque psoriasis. It heard from the clinical specialists that there has been a substantial reduction in hospital admissions for psoriasis as a result of the increasing availability of biological therapies. However, the Committee heard from the clinical specialists that there are currently no treatments that they considered to be effective for people whose psoriasis does not respond adequately to the tumour necrosis factor (TNF) inhibitors (that is, adalimumab, infliximab and etanercept). In addition, with the withdrawal of efalizumab there are no treatment options for people in whom TNF inhibitors are contraindicated, such as people with heart failure or demyelinating disease. The Committee noted that ustekinumab has a different mechanism of action from that of the TNF inhibitors, and heard that the clinical specialists considered that its mechanism of action may be specific in the management of psoriasis. The Committee understood that ustekinumab would be

considered to be of value by people with psoriasis and their clinicians.

4.3 The Committee heard from the clinical specialists and patient experts that ustekinumab may be easier to use than other biological therapies because it is administered subcutaneously just once every 12 weeks after the first 4 weeks. This could enable people to be given the drug during their routine scheduled clinic visits. The Committee was informed by the patient experts that people with psoriasis do not generally have a problem with the frequency of injections, although they prefer less frequent injections. The Committee accepted that the less frequent dosing for ustekinumab, which would allow it to be given during routine scheduled clinic visits, may also help compliance.

4.4 The Committee heard from the clinical specialists that ustekinumab is a new drug that has been given to far fewer people than the other biological therapies, and therefore its long-term safety profile is less certain. Because of this, the specialists considered that the drug may initially be prescribed more cautiously than existing treatments. The Committee also heard from the clinical specialists and patient experts that people with severe psoriasis are often well informed about drug safety and able to consider benefits and risks before starting treatment.

4.5 The Committee considered that the RCTs identified in the manufacturer's submission confirmed the clinical effectiveness of ustekinumab compared with placebo in people with moderate to severe psoriasis. The Committee also considered that ustekinumab had been demonstrated to be more clinically effective than etanercept. It noted, however, that the dosage used for etanercept in the comparative trial was different from that currently recommended in TA103. The Committee heard that the inclusion

criteria used in the clinical trials were representative of people with psoriasis who are being considered for treatment with biological therapies in clinical practice.

4.6 The Committee noted that the manufacturer had conducted a mixed treatment comparison to enable a comparison of ustekinumab with all alternative biological therapies currently available for the treatment of psoriasis. The Committee noted that two analyses had been completed: one analysed data from all patients according to their randomisation, whereas the other analysed data from patients according to a weight-based dosing approach. The Committee noted that the results for both analyses suggested a higher probability of a response after treatment with ustekinumab than with etanercept or adalimumab, but a lower probability of a response compared with infliximab.

4.7 The Committee discussed comments received during consultation on the appraisal consultation document (ACD) suggesting that the efficacy of adalimumab had been underestimated in the mixed treatment comparison because of the possible exclusion of relevant outcome data and the inclusion of a study that had enrolled people with less severe psoriasis. In addition, the Committee discussed the uncertainties about how the analysis had been completed and how it compared with analyses used in previous appraisals. It also considered that randomisation may not have been maintained in the weight-based dosing analysis. The Committee recognised these issues concerning the mixed treatment comparison and took them into account in its decision-making.

4.8 The Committee considered whether the appropriate comparator for ustekinumab should be etanercept given continuously or intermittently, with the latter regimen being specified in TA103 and in the marketing authorisation for etanercept. The Committee heard

from the clinical specialists that biological therapies for psoriasis, including etanercept, are usually used on a continuous basis in clinical practice, although treatment may be interrupted if a person has a sustained remission. The Committee heard that treatment withdrawal was carried out cautiously because a person's condition may deteriorate rapidly and they may subsequently not regain full control of their disease. The Committee heard from the clinical specialists that ustekinumab was likely to be used in a similar way to other biological therapies. The Committee recognised that there is variation in the administration of etanercept in clinical practice, and noted a comment received during consultation on the ACD stating that etanercept is usually given intermittently and only given continuously when required.

4.9 The Committee was aware that the clinical specialists had indicated that ustekinumab may be used after a person's psoriasis had shown an inadequate response to other biological therapies. It was also aware that guidelines in preparation from the British Association of Dermatology might include advice on the sequential use of such therapies. The Committee took note of comments received on the ACD suggesting the use of ustekinumab after the failure of TNF inhibitors. However, no evidence for the use of ustekinumab after an inadequate response to other biological therapies was placed before the Committee. It noted that 40–50% of people in the PHOENIX trials had received previous treatment with biological therapies, but that a person's psoriasis had not necessarily shown an inadequate response to these therapies before the trial use of ustekinumab. Furthermore, data for this subgroup had not been presented separately. Therefore the Committee felt that it could not make any specific recommendations on the use of ustekinumab after a person's psoriasis had failed to respond to other biological therapies.

However, it considered that data on the effectiveness of biological therapies, including ustekinumab, for the sequential treatment of severe plaque psoriasis would be an important part of future assessments.

Cost effectiveness

4.10 The Committee discussed the results of the economic analysis conducted by the manufacturer. It considered the overall approach to modelling adopted by the manufacturer to be appropriate, but noted comments received during consultation on the ACD relating to the potential limitations of the probabilistic sensitivity analyses. The Committee noted the ERG's concerns that no formal subgroup analysis that justified weight-based dosing had been done. It also discussed comments received during consultation on the ACD that other biological therapies might also demonstrate a weight–dose relationship. However, the Committee noted that weight-based dosing is included in the marketing authorisation for ustekinumab and that evidence had been presented for a dose–response relationship with this drug.

4.11 The Committee discussed the assumption in the economic model that 20% of people receiving ustekinumab would weigh more than 100 kg. It recognised that this might be an underestimate, because around 30% of the people included in the PHOENIX trials weighed more than 100 kg. However, the Committee considered that comments received during consultation on the ACD had shown that changing this assumption had minimal impact on estimates of cost effectiveness.

4.12 The Committee noted the assumption in the model that a hospital inpatient period of 21 days would be required for people whose psoriasis had not responded adequately to treatment. The

Committee noted that this assumption had been used in the appraisals of other biological therapies for psoriasis. The Committee heard from the clinical specialists and patient experts that 21 days of inpatient treatment in a year was plausible for a person with severe psoriasis that had not responded adequately to treatment. The Committee also heard from the clinical specialists that the cost of £288 per day for an inpatient stay, as assumed in the model, may be too low. Costs as high as £700 per day may be incurred, but these are usually associated with shorter, more intensive inpatient admissions. Additionally, the Committee heard that the cost of supportive care may be higher than calculated in the model because people may receive methotrexate or ciclosporin even if their disease is not adequately controlled by these treatments. The Committee recognised that the costs were similar to those used in previous appraisals, but was concerned about their accuracy.

4.13 The Committee noted that the economic model assumed that the efficacy of intermittent etanercept was lower than that of continuous etanercept. The Committee was informed that this was based on an RCT showing that, for the outcome measured (PGA score), intermittent etanercept was less effective than continuous etanercept. This difference in effectiveness had then been applied to the PASI response data for continuous etanercept in the mixed treatment comparison in order to determine the efficacy of intermittent etanercept. The Committee considered that an assumption of reduced efficacy of intermittent etanercept may be reasonable, but that the way this had been calculated in the model increased the uncertainty in the results.

4.14 The Committee discussed comments received during consultation on the ACD about the cost of etanercept 25 mg given intermittently.

It recognised that the appraisal of etanercept and efalizumab (TA103) had assumed that the cost of intermittent etanercept 25 mg was 74% that of continuous etanercept. However, in the current appraisal of ustekinumab an estimate of 88% had been used, which reflected that used by another manufacturer in the appraisal of adalimumab. The Committee noted comments received during consultation on the ACD that if the cost of intermittent etanercept 25 mg was 74% of that of continuous etanercept, the ICER for ustekinumab in comparison with intermittent etanercept 25 mg was £68,300 per QALY gained. However, the Committee was mindful of comments from clinical specialists that for people with severe psoriasis, treatment may be given continuously or may have short re-treatment intervals. The Committee recognised that in a scenario where etanercept was given continuously, the manufacturer's analysis suggested that ustekinumab was less costly and more effective.

4.15 The Committee noted that the economic model included a 20% annual dropout rate for people whose psoriasis responded to treatment and that this rate was assumed to be the same for all biological therapies. The Committee heard from the clinical specialists that people on biological therapies do stop treatment because of a reduction in response or adverse events, and that they considered this estimate to be reasonable.

4.16 The Committee was aware that EQ-5D data had not been obtained in the clinical trials, and noted that the manufacturer had mapped DLQI scores to EQ-5D scores to obtain estimates of utility. The Committee noted that this approach had been used in TA103. The Committee recognised that the manufacturer had also provided a secondary analysis using SF-36 values from the PHOENIX-1 trial

transformed into SF-6D scores. The Committee accepted the manufacturer's use of mapping to determine utility estimates.

4.17 The Committee noted that the cost-effectiveness analysis included the patient access scheme. It noted that without the patient access scheme the ICERs for ustekinumab would be £41,000 per QALY gained compared with supportive care, £102,000 per QALY gained compared with intermittent etanercept 25 mg, and £300,000 per QALY gained compared with adalimumab. The Committee therefore concluded that ustekinumab could not be considered a cost-effective use of NHS resources without the patient access scheme. The Committee was reassured that the patient access scheme would remain in place until either a review of the guidance by NICE or the introduction of any new formulations that would render the scheme obsolete, and that it would not be withdrawn without the agreement of NICE and the Department of Health. The Committee concluded that it was reasonable to consider the estimates of cost effectiveness that included the patient access scheme.

4.18 The Committee noted that in the manufacturer's base-case analysis, which included the patient access scheme, ustekinumab had an ICER of £29,600 per QALY gained compared with supportive care, and an ICER of £27,100 per QALY gained compared with etanercept 25 mg given intermittently. The Committee was mindful that this analysis assumed that the cost of intermittent etanercept was 88% of the cost of continuous etanercept. The Committee also noted that the manufacturer's analysis suggested that ustekinumab was less costly and more effective than adalimumab. However, it was aware that revised estimates for the efficacy of adalimumab had been provided during consultation on the ACD, and the resulting ICERs suggested that

ustekinumab was not a cost-effective alternative to adalimumab. The Committee considered that the differences in incremental costs and QALYs between all treatments were small, and that this was particularly the case when considering ustekinumab and adalimumab. This meant that these ICERS were very sensitive to small changes in either costs or QALYs and therefore did not represent stable estimates of cost effectiveness. Therefore the Committee concluded that no robust differences in cost effectiveness between adalimumab and ustekinumab had been shown.

Further considerations and summary

4.19 The Committee considered how the population with severe psoriasis should be defined. It heard from the clinical specialists that a combination of DLQI and PASI scores is used routinely in clinical practice, and agreed that it would be appropriate to define severe disease as a PASI score of 10 or more and a DLQI score of more than 10, in line with TA103. Furthermore, the clinical specialists indicated that the treatment continuation rules defined in section 1.2 of TA103 remain relevant to clinical practice. However, the Committee noted that the response should be measured at 16 weeks for ustekinumab, rather than at 12 weeks as defined for etanercept in TA103, and that this measurement should be carried out before the third (16-week) dose is given.

4.20 The Committee was mindful of the uncertainties in the resource and cost data and the potential methodological limitations of the mixed treatment comparison. The Committee considered that it would be of value to review all of the biological therapies for psoriasis in a multiple technology appraisal. It also noted that data collection, as described in its recommendations for further research (see section 6), would help decisions to be made in future

appraisals. It concluded that the estimates of the cost effectiveness of ustekinumab compared with supportive care were acceptable. It also concluded that, in comparisons of ustekinumab with other biological therapies, the ICERs depended on small differences in costs and benefits that were subject to uncertainty. On balance, the Committee was persuaded that ustekinumab should be recommended as a treatment option for people with severe plaque psoriasis when standard systemic therapies have not produced an adequate response, or if a person is intolerant of or has a contraindication to these therapies.

4.21 The Committee was aware that there might be some situations when the DLQI may not be a clinically appropriate tool to inform a clinician's conclusion about the severity of psoriasis; for example, if a person has physical, sensory or learning disabilities, or communication difficulties that could affect their responses to the questionnaire. The Committee heard from the clinical specialists that the DLQI is now available in more than 50 languages and that this has improved assessment for those people whose first language is not English. The Committee concluded that healthcare professionals should take any physical, sensory or learning disabilities and communication difficulties into account when using the DLQI and make any adjustments they consider appropriate.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding

direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee considered that the following research would be of value:

- Studies comparing ustekinumab and other biological therapies in head-to-head trials, both in people whose psoriasis has shown an inadequate response to the first biological therapy and in people naive to biological therapies. These studies should investigate weight–dose relationships, as far as these can be considered within the marketing authorisations.
- Studies investigating resource use, including frequency and length of hospitalisation and associated costs.
- The collection of data on the use of ustekinumab and other biological therapies as part of the British Association of Dermatologists' Biologics Intervention Register (BADBIR).

7 Related NICE guidance

Published

- Adalimumab for the treatment of adults with psoriasis. NICE technology appraisal guidance 146 (2008). Available from www.nice.org.uk/TA146
- Infliximab for the treatment of adults with psoriasis. NICE technology appraisal guidance 134 (2008). Available from www.nice.org.uk/TA134
- Etanercept and efalizumab for the treatment of adults with psoriasis. NICE technology appraisal guidance 103 (2006). Available from www.nice.org.uk/TA103

8 Review of guidance

8.1 The guidance on this technology will be considered for review in January 2010, at the same time as 'Etanercept and efalizumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 103), 'Infliximab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 134) and 'Adalimumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 146). The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

David Barnett
Chair, Appraisal Committee
August 2009

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, Newcastle University

Dr Jane Adam

Department of Diagnostic Radiology, St George's Hospital, London

Professor AE Ades

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

Dr Amanda Adler

Consultant Physician, Cambridge University Hospitals Trust

Dr Tom Aslan

General Practitioner, Stockwell, London

Dr Matt Bradley

Value Demonstration Director, AstraZeneca

Mrs Elizabeth Brain

Lay member

Dr Robin Carlisle

Deputy Director of Public Health, Rotherham PCT

Professor Karl Claxton

Professor of Health Economics, University of York

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Dr Richard Harling

Director of Public Health, Worcestershire PCT and Worcestershire County Council

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr James Moon

Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr David Newsham

Lecturer (Orthoptics), University of Liverpool

Dr Ann Richardson

Lay member

Mrs Angela Schofield

Chairman, Bournemouth and Poole Teaching PCT

Mr Mike Spencer

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

Professor Iain Squire

Consultant Physician, University Hospitals of Leicester

Mr David Thomson

Lay member

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital, Cambridge

B NICE project team

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

Raphael Yugi and Sally Gallaugher

Technical Leads

Zoe Garrett

Technical Adviser

Bijal Chandarana

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre, The University of Southampton:

- Gospodarevskaya E, Picot J, Cooper K et al. Ustekinumab for the treatment of moderate to severe psoriasis, March 2009

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Janssen-Cilag

II Professional/specialist and patient/carer groups:

- British Association of Dermatologists
- Psoriasis and Psoriatic Arthritis Alliance
- Psoriasis Association
- Royal College of Physicians
- Royal College of Nursing

III Other consultees:

- Department of Health
- Dorset PCT
- Welsh Assembly Government
- Sandwell PCT

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Southampton Health Technology Assessments Centre, The University of Southampton
- National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme
- NHS Quality Improvement Scotland
- Abbott Laboratories
- Merck Serono
- Schering-Plough
- Wyeth Pharmaceuticals

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on ustekinumab for moderate to severe psoriasis by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Alex Anstey, Consultant Dermatologist, nominated by The British Association of Dermatologists – clinical specialist
- Professor Jonathan Barker, Consultant Dermatologist, nominated by The British Association of Dermatologists – clinical specialist
- Mr Ray Jobling, nominated by The Psoriasis Association – patient expert
- Miss Helen McAteer, nominated by The Psoriasis Association – patient expert