NICE National Institute for Health and Care Excellence

Ustekinumab for treating active psoriatic arthritis

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1 Guidance

1.1 Ustekinumab is not recommended within its marketing authorisation for treating active psoriatic arthritis, that is, alone or in combination with methotrexate in adults when the response to previous non-biological disease-modifying antirheumatic drug (DMARD) therapy has been inadequate.

1.2 People currently receiving treatment initiated within the NHS with ustekinumab that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

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2 The technology

2.1 Ustekinumab (Stelara, Janssen) is a monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin-12 (IL-12) and interleukin-23 (IL-23). It is administered by subcutaneous injection. Ustekinumab has a UK marketing authorisation for use alone or in combination with methotrexate 'for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying antirheumatic drug (DMARD) therapy has been inadequate'.

2.2 The summary of product characteristics lists the following common adverse reactions for ustekinumab: dental and upper respiratory tract infections, nasopharyngitis, dizziness, headache, oropharyngeal pain, diarrhoea, nausea, pruritus, back pain, myalgia, arthralgia, fatigue, injection-site erythema and injection-site pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price for ustekinumab is £2147 per 45-mg vial (excluding VAT; British National Formulary edition 66, September 2013). The recommended dose of ustekinumab is an initial dose of 45 mg, followed by a dose 4 weeks later and further doses every 12 weeks thereafter. A dose of 90 mg may be used in people with a body weight over 100 kg. The summary of product characteristics notes that consideration should be given to discontinuing treatment in people whose psoriatic arthritis has shown no response after up to 28 weeks of treatment. The average annual acquisition costs for ustekinumab 45 mg and 90 mg are £10,735 and £21,470 in the first year and £9304 and £18,608 per year thereafter respectively. Costs may vary in different settings because of negotiated procurement discounts.

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3 The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of ustekinumab and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 Evidence on the clinical effectiveness of ustekinumab was taken from 2 clinical studies – PSUMMIT 1 and 2. Both were randomised, double-blind, placebo-controlled, phase III studies conducted in adults with active psoriatic arthritis despite current or previous treatment. The studies were almost identical, except for the previous treatment: PSUMMIT 1 (n=615) included people who had previously received disease-modifying antirheumatic drugs (DMARDs) and/or non-steroidal anti-inflammatory drugs (NSAIDs) only, whereas PSUMMIT 2 (n=312) also included people who had previously received tumour necrosis factor (TNF) alpha inhibitors. People in both trials generally had long-standing moderate to severe active psoriatic arthritis with impaired physical function and high numbers of tender and swollen joints. In both PSUMMIT 1 and 2, approximately 70% of patients had skin disease, and 80–90% of patients had received prior DMARD therapy. Of the 180 people in PSUMMIT 2 who had previously received TNF alpha inhibitors (referred to in this document as 'TNF alpha inhibitor-exposed'), more than half had received at least 2 drugs. In both studies, patients were randomised to ustekinumab 45 mg or 90 mg (administered at 0 and 4 weeks, then every 12 weeks thereafter) or placebo. People in the placebo group switched to receive ustekinumab 45 mg after 16 weeks (if they had less than 5% improvement in both tender and swollen joint counts) or 24 weeks (all others), and people whose disease did not respond to the 45-mg dose of ustekinumab switched to 90 mg after 16 weeks. People in the studies were followed for up to 100 weeks in PSUMMIT 1 and 52 weeks in PSUMMIT 2.

3.2 The primary endpoint in the PSUMMIT 1 and 2 trials was the American College of Rheumatology (ACR) 20 response rate at week 24. This is defined as an improvement of 20% or more in swollen and tender joint counts, and an improvement of 20% or more in 3 of 5 assessments of pain, disease activity and physical function. Secondary endpoints included measures of joint

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symptoms (including modified Psoriatic Arthritis Response Criteria [PsARC] and ACR50/70), skin lesions (Psoriasis Area and Severity Index [PASI]), soft tissue symptoms, radiographic response, and disability and quality of life (Health Assessment Questionnaire Disability Index [HAQ-DI], Dermatology Life Quality Index [DLQI] and 36-item Short-Form Health Survey [SF-36]).

3.3 In both PSUMMIT 1 and 2, ustekinumab was associated with statistically significantly higher rates of ACR20 response at week 24 than placebo. ACR20 response rates in PSUMMIT 1 were 42.4%, 49.5%, 46.0% and 22.8% for ustekinumab 45 mg, ustekinumab 90 mg, ustekinumab 45 mg and 90 mg pooled, and placebo respectively ($p<0.0001$ for ustekinumab compared with placebo). Ustekinumab showed similar effectiveness compared with placebo regardless of prior exposure to TNF alpha inhibitors. ACR20 response rates in PSUMMIT 2 for ustekinumab 45 mg, ustekinumab 90 mg, ustekinumab 45 mg and 90 mg pooled, and placebo respectively were:

- no prior TNF alpha inhibitors: 53.5%, 55.3%, 54.4% and 28.6% ($p\leq0.021$ for ustekinumab compared with placebo)
- TNF alpha inhibitor-exposed: 36.7%, 34.5%, 35.6% and 14.5% ($p\leq0.011$ for ustekinumab compared with placebo).

3.4 Ustekinumab also demonstrated similar efficacy regardless of concomitant methotrexate use. ACR20 response rates in PSUMMIT 1 for ustekinumab 45 mg, ustekinumab 90 mg, ustekinumab 45 mg and 90 mg pooled, and placebo respectively were:

- with concomitant methotrexate: 43.4%, 45.5%, 44.5% and 26.0%
- without concomitant methotrexate: 41.5%, 53.4%, 47.4% and 20.0%.

Corresponding results from PSUMMIT 2 were provided as academic in confidence and therefore cannot be reported here.

3.5 Longer-term analyses of the primary outcome suggested that response rates with ustekinumab were maintained over 52 weeks. Response rates in the placebo arm increased after week 24 because of people switching from placebo to ustekinumab.

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3.6 The results from secondary outcome analyses at week 24 generally supported the conclusions from the ACR20 results; these findings were observed across joint, radiographic, skin, soft tissue and health-related quality of life endpoints, although the results varied between outcomes and between trials and not all outcomes reached statistical significance in all analyses. For example, for all randomised patients in both PSUMMIT 1 and 2, PsARC response rates with ustekinumab (45 mg and 90 mg pooled) and placebo were 58.0% and 35.2% respectively; PASI75 response rates (people who had at least 75% improvement in PASI score) with ustekinumab (45 mg and 90 mg pooled) and placebo were 57.6% and 8.8% respectively. For all randomised patients in PSUMMIT 1, the median HAQ-DI changes from baseline with ustekinumab (45 mg and 90 mg pooled) and placebo were −0.25 and 0.00 respectively ($p<0.001$). For all these examples, results were similar in individual trials and for individual doses. Longer-term analyses of PASI75 responses suggested that response rates with ustekinumab were maintained over 52 weeks. Long-term analyses of other secondary outcomes were provided as academic in confidence and therefore cannot be reported here.

3.7 In the absence of head-to-head randomised controlled trials, the manufacturer presented a mixed treatment comparison using a random-effects model fitted with Bayesian methodology to explore the clinical effectiveness of ustekinumab compared with TNF alpha inhibitors (adalimumab, etanercept, golimumab and infliximab) in people who had not previously received TNF alpha inhibitors (referred to in this document as 'TNF alpha inhibitor-naive'). The manufacturer did not carry out a mixed treatment comparison for the TNF alpha inhibitor-exposed population because PSUMMIT 2 is the only trial to have included this population. The mixed treatment comparison focused on PsARC, PASI75 and PASI90 responses to treatment at weeks 12–16 and 24, which are consistent with the clinical parameters in the economic model. For ustekinumab, patient-level data were extracted from PSUMMIT 1 and 2 for a weight-based dosing subgroup in which patients who weighed 100 kg or less received ustekinumab 45 mg, and patients who weighed more than 100 kg received ustekinumab 90 mg. For the TNF alpha inhibitors, data were taken directly from 7 randomised, double-blind, placebo-controlled studies conducted in people with active psoriatic arthritis. The manufacturer reported that the findings showed that ustekinumab and TNF alpha inhibitors have better outcomes than placebo

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in most analyses. The results of the mixed treatment comparison for PsARC and PASI were marked as academic in confidence and cannot be reported here. It noted that for the analysis of joint symptoms (PsARC), probabilities of response for ustekinumab were lower than for the TNF alpha inhibitors, although the 95% credible intervals for ustekinumab 45 mg overlapped with those of adalimumab, golimumab 50 mg and infliximab. The manufacturer reported that in the analyses of skin symptoms, there may be higher probabilities of response with infliximab (PASI75 and PASI90), golimumab 100 mg (PASI75) and adalimumab (PASI90) compared with other biological drugs, although the credible intervals were overlapping. The manufacturer presented adverse event data from the PSUMMIT studies, 5-year extensions of 4 studies of ustekinumab in psoriasis, the Psoriasis Longitudinal Assessment and Registry (PSOLAR) and the British Society for Rheumatology Biologics Register (BSRBR). The incidence of adverse events in the PSUMMIT studies was similar in the ustekinumab treatment arms compared with the placebo arms. For all randomised patients in PSUMMIT 1 and 2, the incidences were: ustekinumab 45 mg, 48.4%; 90 mg, 49.4%; 45 mg and 90 mg combined, 48.9%; placebo, 47.9%. There were no disproportionate increases in adverse event rates over time. The most common adverse reactions observed with ustekinumab in the PSUMMIT trials included nasopharyngitis, upper respiratory tract infection, headache, arthralgia (joint pain), nausea and diarrhoea. The overall rates of study discontinuation because of adverse events were low (and higher with placebo than with ustekinumab); the rates were 3.4%, 1.5% and 1.5%, for placebo, ustekinumab 45 mg and ustekinumab 90 mg respectively, in the placebo-controlled period. The psoriasis extension studies and register data reported no clear dose–response effect or cumulative exposure effect for ustekinumab, and suggested that the rates of serious adverse events were comparable between ustekinumab and TNF alpha inhibitors.

Cost effectiveness

3.8 The manufacturer presented a de novo economic analysis that assessed the cost effectiveness of ustekinumab compared with TNF alpha inhibitors (in people who were TNF alpha inhibitor-naive) and conventional management without TNF alpha inhibitors (in people who were TNF alpha inhibitor-exposed)

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for treating adults with active psoriatic arthritis for whom the response to previous DMARD therapy has been inadequate. The patient populations were based on the populations in the manufacturer's mixed treatment comparison and PSUMMIT 1 and 2. It was assumed that all patients who weigh less than 100 kg would receive ustekinumab 45 mg, and all those who weigh more than 100 kg would receive ustekinumab 90 mg. The model comprised a short-term decision tree followed by a long-term Markov model with a lifetime (52-year) time horizon. It was similar to the models used in previous NICE appraisals of treatments for psoriatic arthritis. In the decision tree phase, people received initial biological therapy for either 12 weeks (TNF alpha inhibitors) or 24 weeks (ustekinumab). At this point, people who had a PsARC response continued with biological therapy, and those who did not switched to conventional management. All patients then entered the Markov phase of the model. People receiving a biological therapy continued to receive it until they switched to conventional management, either because the biological therapy lacked efficacy or led to adverse events (at a rate of 16.5% per year for all treatments), or they died. No second biological drug was permitted. The model considered costs from an NHS and personal social services perspective, and all costs and health effects were discounted at a rate of 3.5% per year.

3.9 For the TNF alpha inhibitor-naive population, ustekinumab was compared with 4 TNF alpha inhibitors and conventional management, using clinical effectiveness evidence from the mixed treatment comparison. For the TNF alpha inhibitor-exposed population, ustekinumab was compared with conventional management only, because there are no randomised controlled trials of TNF alpha inhibitors in this population. Analyses of this population were based on clinical effectiveness evidence from the TNF alpha inhibitor-exposed sub-population of PSUMMIT 2.

3.10 The model captured health-related quality of life through joint symptoms, disability and skin symptoms (PsARC response, HAQ-DI score and PASI score). People who had a PsARC or PASI response were assumed to have a fixed improvement in HAQ-DI or PASI score respectively. This improvement was maintained until a switch to conventional management, at which point the score returned to its baseline value (rebounded). People who did not have an initial response were assumed to have a smaller improvement in HAQ-DI or

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PASI score until withdrawal of active treatment. Throughout periods of conventional management, people were subject to the natural history of psoriatic arthritis, modelled as a linear increase (worsening) in HAQ-DI over time and a constant PASI score. HAQ-DI and PASI scores were then mapped to EQ-5D using an equation used in previous appraisals of psoriatic arthritis treatments (Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis [NICE technology appraisal guidance 199] and Golimumab for the treatment of psoriatic arthritis [NICE technology appraisal guidance 220]). Costs and disutilities associated with adverse events were not included in the model. Healthcare resource use was estimated based on NHS reference costs, and included resource use associated with biological and conventional treatments (including initial and follow-up consultations and blood tests) and resource use as a function of health state (including hospitalisations, surgical interventions and concomitant medications). The acquisition costs for TNF alpha inhibitors took into account the patient access scheme for golimumab. Administration costs were included for intravenous infliximab only, because all other biological drugs were assumed to be administered by subcutaneous injection at no cost to the NHS.

3.11 A number of iterations of the economic model were presented by the manufacturer: the first in its original submission (hereafter referred to as the 'original' model), the second corrected after the clarification stage (hereafter referred to as the 'updated' model), and the third corrected during consultation (hereafter referred to as the 'final' model). The original model was used to develop a base case, deterministic and probabilistic sensitivity analyses and a series of scenario analyses; the results of the base case and scenario analyses were superseded by the updated and final models so are not reported here. The updated model incorporated corrections requested by the ERG during clarification, including amendments to the probability distributions for some variables and to the costs associated with psoriatic arthritis. The manufacturer used this model to develop an updated base case and updated scenario analyses. The final model submitted during consultation corrected an error identified by the manufacturer and a manufacturer of a comparator drug during consultation affecting the acquisition cost of golimumab 100 mg. The cost-effectiveness evidence presented here for the TNF alpha inhibitor-naive population is based on the results of the final model, which superseded the

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previous models. The cost-effectiveness evidence presented here for the TNF alpha inhibitor-exposed population is based on the updated model (because the TNF alpha inhibitors were not included as comparators in this population, and therefore the golimumab error did not apply).

3.12 In the TNF alpha inhibitor-naive population (final model, probabilistic results), ustekinumab was associated with total costs of £70,249 and a total of 6.23 QALYs. Adalimumab was associated with costs of £64,487 and 6.42 QALYs, and therefore dominated ustekinumab (that is, adalimumab was more effective and less expensive). Adalimumab, in turn, was associated with an additional £31,476 in costs and 1.76 QALYs compared with conventional management, giving an incremental cost-effectiveness ratio (ICER) of £17,868 per QALY gained. The manufacturer also presented pairwise comparisons between ustekinumab and conventional management (final model, probabilistic results): ustekinumab provided 1.57 additional QALYs compared with conventional management, at an additional cost of £37,239, giving an ICER of £23,723 per QALY gained. The deterministic sensitivity analyses (original model) showed that the results were most sensitive to the change in HAQ-DI score over time associated with the natural history of psoriatic arthritis, the proportion of people who had a PsARC response, and the HAQ-DI change associated with PsARC response.

3.13 In the TNF alpha inhibitor-exposed population (updated model, probabilistic results), ustekinumab provided an additional 1.41 QALYs compared with conventional management, at an additional cost of £41,199, to give an ICER of £29,132 per QALY gained compared with conventional management. The probabilistic sensitivity analysis (original model) indicated there was a 0% and 67% probability of ustekinumab being cost effective compared with conventional management if the maximum acceptable ICERs were £20,000 and £30,000 per QALY gained respectively. The deterministic sensitivity analyses (original model) showed that the results were most sensitive to the HAQ-DI score change with the natural history of psoriatic arthritis and the HAQ-DI change associated with a PsARC response.

3.14 The manufacturer presented a series of scenario analyses for both the TNF alpha inhibitor-naive and exposed populations (updated model). These

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explored structural assumptions in the model around the treatment continuation rule (timing and criteria), progression of psoriatic arthritis, and utility and clinical effectiveness estimates. In the TNF alpha inhibitor-naive population, all scenario analyses indicated that ustekinumab was more expensive and less effective than adalimumab. Ustekinumab was associated with probabilistic ICERs compared with conventional management ranging from £21,628 to £31,469 per QALY gained. In the scenario in which treatment response was assessed at week 24 for all treatments, ustekinumab was associated with additional costs of £38,222 and an additional 1.28 QALYs compared with conventional management, giving a probabilistic ICER of £29,808 per QALY gained for ustekinumab compared with conventional management. In scenario analyses for the TNF alpha inhibitor-exposed population, ustekinumab was associated with probabilistic ICERs compared with conventional management ranging from £27,606 to £40,019 per QALY gained. In the scenario in which treatment response was assessed at week 24 for all treatments, ustekinumab was associated with additional costs of £43,064 and an additional 1.12 QALYs compared with conventional management, giving a probabilistic ICER of £38,516 per QALY gained for ustekinumab compared with conventional management.

ERG's critique and exploratory analyses for the manufacturer's submission

3.15 The ERG carried out exploratory analyses to test whether the clinical effectiveness of ustekinumab was influenced by prior TNF alpha inhibitor treatment or ustekinumab dose. It stated that there is no convincing evidence of a substantial difference in the effectiveness of ustekinumab between people who have and people who have not previously received TNF alpha inhibitors, and that treatment effects were not statistically significantly different between ustekinumab doses.

3.16 The ERG identified a number of limitations in the evidence available from the PSUMMIT studies. The switch from placebo to ustekinumab at weeks 16 and 24 provides a short-term comparison for a chronic condition such as psoriatic arthritis. Analyses of TNF alpha inhibitor-exposed patients included only the 180 patients, who had previously received varying numbers of TNF alpha

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inhibitors for varying durations. The ERG emphasised that the analyses of PSUMMIT 2 did not distinguish between people who had received 1, 2, 3 or more prior TNF alpha inhibitors, and so did not differentiate people who had tried just some of the available TNF alpha inhibitors from people for whom TNF alpha inhibitors as a class had failed. The ERG considered that the data on patients whose disease was truly TNF alpha inhibitor refractory were scarce. It was also noted that for many of the secondary outcomes (DLQI, SF-36 and radiographic scores), baseline scores were not reported, hindering the interpretation of the results.

3.17 The ERG considered that, despite some heterogeneity between trials, the mixed treatment comparison was appropriate to undertake and the results were robust. It did not consider that the weight-based dosing subgroup matched the marketing authorisation, and noted that this led to exclusion of a large amount of data. However, the ERG noted that an additional analysis including all patients from PSUMMIT 1 and 2 provided fairly similar results to the weight-based analysis. The ERG noted that overall, the mixed treatment comparison found that ustekinumab had the lowest or one of the lowest response rates for PASI75, PASI90 and PsARC.

3.18 The ERG noted that the manufacturer's economic model was similar to those used in previous appraisals of etanercept, infliximab and adalimumab (NICE technology appraisal guidance 199) and golimumab (NICE technology appraisal guidance 220) for treating psoriatic arthritis, although it had a longer time horizon (52 years compared with 40 years). It considered many of the key assumptions used in the model to be broadly acceptable, including change in PASI score with biological treatment, rebound effect on treatment withdrawal, withdrawal rates in the TNF alpha inhibitor-naive population, exclusion of disutilities and costs for adverse events, the equation used to map HAQ-DI and PASI to EQ-5D, resource use, drug and health state costs, and the approach to deterministic sensitivity analysis. The ERG cautioned that the results of the model should be interpreted with care, specifically the pairwise ICERs for ustekinumab compared with conventional management in the TNF alpha inhibitor-naive population; it considered that these ICERs represent a scenario in which ustekinumab is the only alternative to conventional management, which is unrealistic.

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3.19 The ERG highlighted weaknesses in the clinical effectiveness parameters used in the model. It noted that the manufacturer used a mixture of results from the mixed treatment comparison for the effectiveness of TNF alpha inhibitors and PSUMMIT results for the effectiveness of ustekinumab to obtain HAQ-DI score changes, and considered that there were limitations to this approach. In addition, PsARC response rates for ustekinumab based on the weight-based dosing subgroup resulted in a loss of data. The ERG considered both of these issues in exploratory analyses (see sections 3.23 and 3.24). Furthermore the ERG queried the model assumption that people receiving conventional management did not have any improvement in PASI, whereas in clinical practice skin symptoms often respond well to DMARDs.

3.20 The ERG noted the simplifying assumption in the model that people switched to conventional management after failure of the intervention being analysed, and did not receive subsequent biological therapies. Thus, the costs and benefits associated with subsequent lines of biological treatment were not included in the model. In clinical practice in the UK, most people whose disease has failed to respond to 1 TNF alpha inhibitor would be considered for subsequent-line TNF alpha inhibitor treatment.

3.21 The ERG emphasised the uncertainties about the natural history progression of psoriatic arthritis scores during conventional management. This is a key driver of the model. The assumptions underlying the gradual increase in HAQ-DI scores during conventional management were consistent with previous submissions. However, the ERG noted that the estimate for the rate of progression was prepared from limited data in 2009 but not updated. It also queried whether the assumptions about rebound and progression of arthritis symptoms taken from models of TNF alpha inhibitors were applicable to ustekinumab, given its different mechanism of action.

3.22 The ERG highlighted that the TNF alpha inhibitor-exposed population has not been considered in previous appraisals, and noted some uncertainties in the model for this population. By comparing ustekinumab with conventional management, the manufacturer made no distinction between people whose disease had not responded to 1, 2, 3 or more TNF alpha inhibitors. That is, it did not differentiate people who had tried just some of the available TNF alpha

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inhibitors from people for whom TNF alpha inhibitors as a class had failed. In clinical practice in the UK, most people whose disease has failed to respond to 1 TNF alpha inhibitor would be considered for subsequent-line TNF alpha inhibitor treatment. The ERG therefore considered the manufacturer's model to have severe limitations, noting that ustekinumab should be compared with other TNF alpha inhibitors in the TNF alpha inhibitor-exposed population. The ERG further noted that much of the evidence informing the model was drawn from people who had not received prior TNF alpha inhibitor therapy. In particular, estimates for the natural history progression of HAQ-DI (a key driver of the model), mortality rates and treatment withdrawal rates were based on TNF alpha inhibitor-naive populations. It queried whether these assumptions were applicable to the TNF alpha inhibitor-exposed population.

3.23 The ERG carried out exploratory analyses in both the TNF alpha inhibitor-naive and TNF alpha inhibitor-exposed populations. These explored the sensitivity of the manufacturer's model to assumptions about weight-based dosing, HAQ-DI rebound and natural history progression, the time horizon, the timing of treatment response assessment, and the inclusion of phototherapy. In the TNF alpha inhibitor-naive population, the ERG's exploratory analyses indicated that, in the incremental analysis (comparing ustekinumab, TNF alpha inhibitors and conventional management), ustekinumab remained dominated in all modelled scenarios. Probabilistic ICERs compared with conventional management ranged from £22,455 to £55,029 per QALY gained. In particular, the ERG's analyses indicated that assessing the response to treatment at week 24 for both ustekinumab and conventional management increased the ICER by £6987 per QALY gained, compared with the base case. The ERG presented a preferred base case for the TNF alpha inhibitor-naive population, based on what it considered to be the most plausible assumptions. This consisted of the manufacturer's updated model (see section 3.12), with additional corrections added by the ERG (including amendments to the health state costs, probability distributions and baseline PASI and HAQ-DI scores), applying the weight-based dosing assumption to ustekinumab 90 mg only, and using HAQ-DI scores drawn from an update of the mixed treatment comparison developed by the ERG for the appraisal of golimumab for treating psoriatic arthritis (NICE technology appraisal guidance 220). In this analysis, ustekinumab was dominated by adalimumab. Compared with conventional

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management, ustekinumab was associated with additional costs of £37,123 and an additional 1.6 QALYs, giving a probabilistic ICER compared with conventional management of £23,246 per QALY gained.

3.24 The ERG also presented exploratory analyses in the TNF alpha inhibitor-exposed population. In these exploratory analyses, ustekinumab was associated with probabilistic ICERs compared with conventional management ranging from £28,670 to £69,139 per QALY gained. The ERG conducted an exploratory sequencing analysis for the TNF alpha inhibitor-exposed population, to examine the cost effectiveness of ustekinumab compared with TNF alpha inhibitors, when used as second-line treatments after failure of first-line TNF alpha inhibitors. The ERG presented 3 scenarios for the sequencing analysis: 2 in which first-line treatments failed because of lack of effectiveness (the first based on evidence from PSUMMIT 2, and the second based on the ERG's estimates) and a third in which first-line treatments failed because of adverse events. In the first scenario, ustekinumab was associated with ICERs of £32,818 per QALY gained (compared with adalimumab, when etanercept was used as first-line treatment) to £37,738 per QALY gained (compared with etanercept, when golimumab or adalimumab were used as first-line treatment), and in the other 2 scenarios it was dominated by other treatments. However, the ERG stressed that this exploratory analysis was based on numerous assumptions and was subject to considerable uncertainty. The ERG did not present a preferred base case for the TNF alpha inhibitor-exposed population because of the uncertainty remaining in the model.

Manufacturer's additional analyses provided during consultation

3.25 In response to consultation, the manufacturer submitted additional evidence exploring the cost effectiveness of the 45 mg dose of ustekinumab alone, for both the TNF alpha inhibitor-naive and the TNF alpha inhibitor-exposed populations. The analyses for the TNF alpha inhibitor-naive population were based on the manufacturer's final model (that is, they incorporated the correct acquisition cost of golimumab). The manufacturer noted that the marketing authorisation permits, but does not require, the use of ustekinumab 90 mg for

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people who weigh more than 100 kg. Consequently, it is a possibility that using ustekinumab 45 mg for all patients could be considered.

3.26 In the base-case analysis for the TNF alpha inhibitor-naive population, ustekinumab 45 mg was associated with the lowest costs and the fewest QALYs of all the biological treatments. The probabilistic results indicated that the total costs associated with conventional management were £33,048, and this treatment provided a total of 4.60 QALYs. Ustekinumab was associated with total costs of £62,286 and 6.18 QALYs, giving a probabilistic ICER for ustekinumab compared with conventional management of £18,517 per QALY gained. In this analysis, adalimumab was the next most costly biological drug, with total costs of £64,459 and providing a total of 6.37 QALYs. Adalimumab therefore had an ICER compared with conventional management of £17,804 per QALY gained, and consequently ustekinumab was extendedly dominated by conventional management and adalimumab; that is, ustekinumab was less costly and less effective than adalimumab, but had a higher ICER compared with conventional management than did adalimumab.

3.27 In the base-case probabilistic analysis for the TNF alpha inhibitor-exposed population, ustekinumab 45 mg was associated with costs of £68,037 and a total of 4.28 QALYs, giving an ICER of £21,789 per QALY gained compared with conventional management. The manufacturer also presented a series of scenario analyses for ustekinumab 45 mg alone and replicated the ERG's exploratory sequencing analysis. These scenario analyses explored the impact of key assumptions in the model on the cost effectiveness of ustekinumab.

ERG's critique of the manufacturer's additional analyses

3.28 After consultation, the ERG submitted a critique of the manufacturer's additional analyses exploring the cost effectiveness of ustekinumab 45 mg alone, and carried out further exploratory analyses using this model. The ERG noted that in principle the scenario in which all patients receive ustekinumab 45 mg is reasonable to explore, but highlighted that there is uncertainty about the validity of this scenario in clinical practice. Clinical advisers to the ERG highlighted that even if 45 mg is used as a starting dose, clinicians are likely to use 90 mg as a treatment option for certain patients. The ERG also noted that

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the clinical effectiveness inputs into the model for ustekinumab 45 mg were based on patients who weighed less than 100 kg. The ERG noted that if evidence from the intention-to-treat population from the PSUMMIT studies were used (that is, all people who were randomised to the 45 mg dose in these studies, regardless of weight), this would have minimal impact on the cost-effectiveness results. The ERG applied the 45 mg dosing assumption to its preferred base case for the TNF alpha inhibitor-naive population (see section 3.23), along with the manufacturer's correction of the cost of golimumab, and noted that the results were generally similar to those presented by the manufacturer. For the TNF alpha inhibitor-exposed population, the ERG confirmed that the manufacturer had correctly replicated its exploratory sequencing analysis, although it emphasised that this analysis was highly uncertain because it was based on numerous assumptions.

Further evidence

3.29 Based on a comment received during consultation from a manufacturer of a comparator drug, further evidence was identified by the technical team that provided long-term analyses of the change from baseline in HAQ-DI and radiographic scores with ustekinumab compared with placebo (presented in 2 abstracts and a press release; Kavanaugh et al. 2013, McInnes et al. 2013 and Johnson and Johnson 2013). In a pre-specified pooled analysis of the radiographic scores in PSUMMIT 1 and 2, the mean changes from baseline to week 24 were 0.40, 0.39 and 0.97 (ustekinumab 45 mg, ustekinumab 90 mg and placebo respectively). The mean changes from baseline to week 52 were 0.58, 0.65 and 1.15 (ustekinumab 45 mg, ustekinumab 90 mg and patients randomised to placebo respectively), indicating that ustekinumab inhibited radiographic progression compared with placebo and that this inhibition was continued at week 52. Data from the PSUMMIT 1 trial alone were consistent with the pooled analysis. However, in PSUMMIT 2 alone there was no statistically significant difference in radiographic progression between ustekinumab and placebo; the manufacturer noted that the studies were not individually powered to detect differences in radiographic progression. A long-term analysis of HAQ-DI scores in PSUMMIT 1 indicated that the mean changes from baseline to 52 weeks were −0.34, −0.43 and −0.37 in patients randomised to ustekinumab 45 mg, ustekinumab 90 mg and placebo

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respectively, and the mean changes from baseline at 100 weeks were −0.36, −0.45 and −0.36 (ustekinumab 45 mg, ustekinumab 90 mg and patients randomised to placebo respectively). Long-term analyses of HAQ-DI scores in PSUMMIT 2 were not available at the time of the appraisal.

3.30 Full details of all the evidence are in the manufacturer's submission and the ERG report.

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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 psoriatic arthritis 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.

4.2 The Committee considered the current treatment pathway for people with psoriatic arthritis. It heard from clinical specialists that treatment of psoriatic arthritis follows current NICE guidance: after initial treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs), most people will be treated with a tumour necrosis factor alpha inhibitor (TNF alpha inhibitor). The Committee heard from patients and clinical specialists that TNF alpha inhibitors are the only class of treatments with robustly demonstrated efficacy, because conventional management with DMARDs (such as methotrexate) does not appear to provide substantial benefits for joint-related aspects of psoriatic arthritis. The Committee noted that Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (NICE technology appraisal guidance 199) and Golimumab for the treatment of psoriatic arthritis (NICE technology appraisal guidance 220) recommend TNF alpha inhibitor therapy for people with psoriatic arthritis if the person has peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and the psoriatic arthritis has not responded to adequate trials of at least 2 standard DMARDs (individually or in combination). The guidance also recommends that treatment should normally be started with the least expensive drug (taking into account administration costs, required dose and price per dose), and this may need to be varied for individual patients because of differences in the method of administration and treatment schedules. It heard from clinical specialists that the sequential use of TNF alpha inhibitors is established practice in the NHS. Therefore, if the condition fails to respond to, or loses response to, an initial TNF alpha inhibitor or if the TNF alpha inhibitor causes adverse reactions, a second TNF alpha inhibitor will often be used. The Committee heard from the clinical specialists that they would consider TNF alpha inhibitor treatment to have failed if the person had ongoing joint pain and inflammation despite treatment. The Committee heard from the clinical

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specialists and patient experts that although the availability of second-line TNF alpha inhibitors varies across the UK, the sequential use of TNF alpha inhibitors is extensive. The patient expert emphasised that when a TNF alpha inhibitor is withdrawn because of loss of effectiveness or adverse reactions, the detrimental effect on the patient can be substantial if a subsequent TNF alpha inhibitor is not available. In light of comments received during consultation, the Committee noted that the NICE commissioning guide Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology does not explicitly recommend sequential use of TNF alpha inhibitors in psoriatic arthritis, but considered that both the guide and the published technology appraisals do not preclude this use. The Committee acknowledged the variation in practice across the country, but concluded that the sequential use of TNF alpha inhibitors is established practice in the NHS.

4.3 The Committee considered the likely place of ustekinumab in managing psoriatic arthritis. It heard from clinical specialists that if ustekinumab were to be used in people with prior TNF alpha inhibitor exposure, it might be used after 1, 2 or more TNF alpha inhibitors, depending on person-specific factors such as the reason for withdrawing the previous TNF alpha inhibitor and individual preferences. For example, if the previous TNF alpha inhibitor had no effect or caused class-related adverse reactions, ustekinumab may be used in preference to another TNF alpha inhibitor, whereas if the previous TNF alpha inhibitor loses efficacy over time, another TNF alpha inhibitor might be chosen before ustekinumab. The Committee concluded that the most appropriate comparators for ustekinumab in most people with psoriatic arthritis would be TNF alpha inhibitors, both in people who have not received prior TNF alpha inhibitors (referred to in this document as 'TNF alpha inhibitor-naive') and in those who have previously received TNF alpha inhibitor therapy (referred to in this document as 'TNF-alpha inhibitor exposed').

4.4 The Committee heard from the clinical specialists that there is a group of people with psoriatic arthritis for whom TNF alpha inhibitors are not suitable, because of contraindications such as heart failure or demyelination or because of failure of TNF alpha inhibitors as a class. For these people there is a considerable unmet need. It understood that this affects a number of people, and that for people in this situation there are no effective treatment options.

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Clinical specialists considered that ustekinumab has the potential to offer an innovative treatment option to fulfil this need. The Committee acknowledged that this represents a distinct group with an important unmet need that warrants additional consideration. During consultation, the Committee heard from a manufacturer of a comparator drug that the contraindications for ustekinumab and TNF alpha inhibitors are relatively similar. It therefore considered that the number of people who had not received TNF alpha inhibitor therapy (that is, who were TNF alpha inhibitor-naive), for whom TNF alpha inhibitors as a class were contraindicated and for whom ustekinumab might be appropriate was unknown but may be relatively small. The Committee concluded that conventional management would be an appropriate comparator in people in whom TNF alpha inhibitors were contraindicated and in people whose condition failed to respond to TNF alpha inhibitors as a class.

4.5 The Committee understood that psoriatic arthritis is a lifelong condition that has a serious impact on people's quality of life. It heard from the patient expert that psoriatic arthritis can develop at a young age, and affects all aspects of a person's life including education, work, self-care, and social and family life. The Committee heard from the patient expert that skin symptoms can have a major psychological impact, and that the joint symptoms have an even greater impact on the psychological and functional aspects of living with this chronic condition. The Committee recognised the potential value of additional treatment options for people with psoriatic arthritis.

Clinical effectiveness

4.6 The Committee reviewed the overall clinical effectiveness of ustekinumab. It noted that the evidence for the clinical effectiveness of ustekinumab had been taken from 2 randomised placebo-controlled trials (PSUMMIT 1 and 2), and acknowledged the need for head-to-head studies between ustekinumab and TNF alpha inhibitors for psoriatic arthritis. The Committee considered that the evidence suggested that ustekinumab is more effective than placebo after 24 weeks of treatment across a number of joint, skin and soft tissue outcomes. It considered that although the effect is likely to persist for up to 1 year, there is some uncertainty about this because in the trials people switched from placebo to ustekinumab at week 24. The Committee heard from clinical specialists that

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ustekinumab appeared to be effective across a wide range of skin and joint outcomes and also soft tissue conditions associated with psoriatic arthritis. The Committee also noted that the results from the PSUMMIT studies suggested there was no statistically significant difference in the clinical effectiveness of ustekinumab compared with placebo between TNF alpha inhibitor-naive and TNF alpha inhibitor-exposed populations for the Psoriatic Arthritis Response Criteria (PsARC) response. The Committee concluded that ustekinumab is clinically effective compared with conventional management, in both TNF alpha inhibitor-naive and TNF alpha inhibitor-exposed populations, but acknowledged that there remains some uncertainty about the long-term effects of ustekinumab.

4.7 The Committee considered in detail the evidence on the effect of ustekinumab on radiographic outcomes at 24 weeks and 52 weeks. It noted that the effect of ustekinumab compared with placebo appeared to be different to what has been previously observed in clinical trials of golimumab compared with placebo. In particular, ustekinumab appeared to slow the increase (progression) in radiographic score compared with placebo, whereas golimumab (NICE technology appraisal guidance 220) had previously been shown to reduce radiographic score from baseline. Furthermore, ustekinumab had not shown a statistically significant difference from placebo in the PSUMMIT 2 study (which included a TNF alpha inhibitor-exposed population). The Committee heard from the manufacturer that interpretation of these findings was subject to 4 key difficulties – firstly, that changes in radiographic score were very small, secondly that the individual studies were not powered for this end point, thirdly that there was a high level of missing data in the placebo arm because of patient withdrawal (approximately 23%), and finally that the link between radiographic score and quality of life in psoriatic arthritis is uncertain. The Committee considered that the evidence on radiographic progression with ustekinumab must be interpreted with caution and it was not able to reach a conclusion on the effectiveness of ustekinumab compared with TNF alpha inhibitors for this outcome. However, it concluded that these results provide some evidence to suggest care is needed when applying assumptions based on TNF alpha inhibitors to ustekinumab, and noted that this may affect the validity of some assumptions in the manufacturer's economic model (see section 4.12).

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4.8 The Committee considered the clinical effectiveness of ustekinumab compared with TNF alpha inhibitors in the TNF alpha inhibitor-naive population. The Committee reviewed the findings of the manufacturer's mixed treatment comparison (see section 3.7), and noted that the analysis explored the 3 outcomes used as clinical effectiveness inputs in the economic model (Psoriasis Area and Severity Index [PASI] 75, PASI90 and PsARC response rates). It discussed this analysis with the clinical specialists, and was aware of the limitations of the mixed treatment comparison. The Committee concluded that ustekinumab appeared to be less effective than TNF alpha inhibitors for PASI75, PASI90 and PsARC response, particularly for the joint outcome.

4.9 The Committee also considered the clinical effectiveness of ustekinumab compared with TNF alpha inhibitors in the TNF alpha inhibitor-exposed population. The Committee was aware that there is no clinical trial evidence from which to compare ustekinumab and TNF alpha inhibitors, and so considered the effectiveness of ustekinumab and TNF alpha inhibitors compared with conventional management. Although in the PSUMMIT trials there was no difference in clinical effectiveness between TNF alpha inhibitor-naive and TNF alpha inhibitor-exposed populations in terms of PsARC response, the Committee heard from the clinical specialists that evidence presented at a recent conference suggested that the effectiveness of ustekinumab measured using the American College of Rheumatology (ACR) criteria may decrease with increasing numbers of prior TNF alpha inhibitors. The clinical specialists noted that the diminishing effectiveness of ustekinumab in TNF alpha inhibitor-exposed populations is broadly consistent with clinical experience with the TNF alpha inhibitors, which appear to show diminishing effectiveness as the number of prior therapies increases. However, the Committee also heard from the clinical specialists that there is some uncertainty about the size of the diminishing effect: the Committee heard estimates for the response rate with second-line TNF alpha inhibitors ranging from 20% to 70%, although comments received during consultation from a manufacturer of a comparator drug (including evidence from a randomised controlled trial of certolizumab pegol and open-label and observation studies of adalimumab) suggested that the lower estimates in this range may be too low. The Committee also considered whether there may be any variation in clinical effectiveness depending on the reason for withdrawal of the first TNF alpha

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inhibitor (for example, initial lack of efficacy, gradual loss of efficacy over time, or adverse reactions), but it acknowledged that there was not enough evidence for this aspect to be considered further. The Committee concluded that there is still uncertainty about the relative effectiveness of ustekinumab and TNF alpha inhibitors in people who have previously received TNF alpha inhibitors.

4.10 The Committee queried whether both the 45-mg and 90-mg doses of ustekinumab might potentially be used in clinical practice, and if so how the doses might be used. The Committee noted that the marketing authorisation for ustekinumab in psoriatic arthritis indicates that 45 mg may be used for all patients and 90 mg may be considered in people who weigh more than 100 kg, concluding that this permits, but does not require, a weight-based dosing strategy. The Committee also noted that it had not been shown detailed evidence on the relative effectiveness of the 2 doses in people of different weights. The Committee considered the evidence in the European Public Assessment Report published by the European Medicines Agency (EMA), which noted that systemic exposure to ustekinumab (that is, the concentration of ustekinumab in the serum) is similar in people who weigh more than 100 kg and receive ustekinumab 90 mg, compared with people who weigh less than 100 kg and receive ustekinumab 45 mg. Moreover, the EMA noted that the efficacy of ustekinumab 90 mg (in terms of ACR20 response) was higher than ustekinumab 45 mg, particularly in people who weigh more than 100 kg, in the PSUMMIT 1 study, although not in PSUMMIT 2. The Committee heard from the manufacturer that the dose–response effect based on weight for psoriatic arthritis may not be as strong as observed in psoriasis and that the differences between doses were not statistically significant. The Committee also considered evidence from the ERG, which suggested that there was no statistically significant difference in clinical effectiveness between the higher and lower doses, although it was noted that this did not imply the doses are equivalent. The Committee heard from clinical specialists that if ustekinumab were recommended, they would anticipate using both the 45-mg and 90-mg doses in clinical practice (rather than just the 45-mg dose). The Committee acknowledged that there is no clear evidence to support the use of a strict weight-based dosing strategy, although it concluded that both the 45-mg and 90-mg doses would be expected to be used in clinical practice.

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Cost effectiveness

4.11 The Committee considered the structure, assumptions and results in the manufacturer's economic model and the critique presented by the Evidence Review Group (ERG). In particular, it discussed key assumptions about the improvement, rebound and progression of joint symptoms, the effect of conventional management on skin symptoms, the use of the utility equation, the timing of the assessment of response and the sequencing of biological treatments in the TNF alpha inhibitor-exposed population. The Committee then reviewed the effect of these assumptions on the cost-effectiveness estimates for ustekinumab.

4.12 The Committee noted that the assumptions about the improvement, rebound and progression of joint symptoms (as captured using the Health Assessment Questionnaire Disability Index [HAQ-DI]) were key drivers of the economic model. It noted that the approach used in the manufacturer's model (whereby HAQ-DI improved by a fixed amount, giving an improved HAQ-DI score that was maintained at a constant level for the duration of biological treatment, rebounded after treatment withdrawal and then gradually deteriorated during conventional management [see section 3.10]) was consistent with the models used in previous appraisals of TNF alpha inhibitors for psoriatic arthritis (etanercept, infliximab and adalimumab [NICE technology appraisal guidance 199] and golimumab [NICE technology appraisal guidance 220]). It heard from the clinical specialists that HAQ-DI is an acceptable and sensitive treatment outcome measure. The clinical specialists noted that the HAQ-DI rebound effect on withdrawal of TNF alpha inhibitors is not necessarily immediate, but may be associated with a lag of approximately 6 to 12 months, which may also apply to ustekinumab. Furthermore, the Committee considered it possible that the assumption that people experience a fixed improvement in HAQ-DI that is maintained during treatment may not apply to ustekinumab, because it has a different mechanism of action to TNF alpha inhibitors. The observed differences in radiographic progression (see section 4.6) may provide some support for this suggestion. Conversely, the Committee understood that the radiographic progression results must be interpreted with caution, and also noted evidence from the PSUMMIT 1 study on HAQ-DI scores with ustekinumab after 52–100 weeks that did not suggest a substantial worsening

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over time (see section 3.29; long-term analyses of HAQ-DI scores in PSUMMIT 2 were not available at the time of the appraisal). It considered it possible that there may be some worsening of HAQ-DI score during ustekinumab treatment, and that this would be likely to decrease the cost effectiveness of ustekinumab, although the size of this effect is unknown. The Committee acknowledged that there is a lack of robust evidence to reliably inform these assumptions, but would have liked to have seen an assessment of the effect on the model results of worsening HAQ-DI over time during ustekinumab treatment. The Committee concluded that there remains considerable uncertainty as to how well the HAQ-DI assumptions apply to ustekinumab, but considered that the assumptions in the model were a sufficient basis on which to make a decision.

4.13 The Committee considered the way in which the effect of conventional management on skin symptoms had been modelled. It noted that the manufacturer's model assumed that conventional management strategies did not affect skin symptoms, but heard from the ERG that its clinical adviser stated that in practice DMARDs such as methotrexate often improve psoriasis symptoms. During consultation, the Committee received additional information from a manufacturer of a comparator drug on the effect of conventional management on skin symptoms, taken from a study of adalimumab. The Committee noted that it would have liked to have seen an exploration of the effect of conventional management on skin symptoms. The Committee considered that the manufacturer's model had underestimated the clinical benefits of conventional management, and so had underestimated the pairwise incremental cost-effectiveness ratios (ICERs) both for ustekinumab and for TNF alpha inhibitors, compared with conventional management. The Committee noted that the size of the effect on the ICER is unknown, and concluded that the most plausible ICER for ustekinumab compared with conventional management would be higher than the manufacturer's base case.

4.14 The Committee noted that the manufacturer's base-case analysis was based on utility scores derived using a previously published equation used in the appraisals of etanercept, infliximab and adalimumab (NICE technology appraisal guidance 199) and golimumab (NICE technology appraisal guidance 220) for the treatment of psoriatic arthritis. However, it also noted that health-

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related quality of life evidence had been captured directly in the PSUMMIT studies, through the 36-item Short-Form Health Survey (SF-36). The Committee understood that the manufacturer used the SF-36 data to derive an alternative utility equation, and that the impact of this approach on the model results was examined in a sensitivity analysis. However, it further noted that this alternative utility equation was subject to uncertainty, because of a need to map from SF-36 to EQ-5D using evidence from people without psoriatic arthritis. The Committee considered that all health-related quality of life evidence from the clinical trials – including the SF-36 data – should ideally be used if possible. However, because of the uncertainty in the newer utility equation, and the fact that the effectiveness of ustekinumab in the PSUMMIT trials was captured through the HAQ-DI and PASI scores, the Committee concluded that using the previously published equation would be more appropriate and would support a consistent approach between appraisals.

4.15 The Committee considered the appropriateness of assessing treatment responses at week 12 for TNF alpha inhibitors and conventional management and week 24 for ustekinumab. It heard from the clinical specialists that there is some uncertainty about when ustekinumab begins to take effect, although the onset of action may be slower than TNF alpha inhibitors. The clinical specialists stated that DMARDs such as methotrexate often show little or no effect after 12 weeks, and if they do provide benefits these may arise with longer treatment. It was suggested by the clinical specialists that there is no specific reason why ustekinumab and TNF alpha inhibitors should be assessed at the same time point, because they are different treatments, although the use of different time points in the economic model is likely to favour ustekinumab. The Committee heard during consultation that the British Society for Rheumatology guidelines define a therapeutic trial of DMARDs as at least 12 weeks, although it noted that this did not preclude assessment of response at 24 weeks. The Committee concluded that for pairwise comparisons between ustekinumab and conventional management, the treatment response should have been assessed at the same time point. The Committee had a preference for assessing treatment response at 24 weeks for both ustekinumab (in line with its summary of product characteristics and the primary efficacy analysis of the PSUMMIT 1 and 2 studies) and conventional management, and noted that this assumption increased the ICER for ustekinumab.

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4.16 The Committee considered the impact of sensitivity analyses and scenario analyses on the results of the economic model. It noted that the manufacturer and ERG presented a number of analyses (see sections 3.14 and 3.23). The Committee noted that the model was highly sensitive to assumptions about HAQ-DI score. In addition to the key assumptions explored in sections 4.12–15 the Committee noted that there were further assumptions that were subject to uncertainty, but which had little impact on the results of the model. It noted that the manufacturer's weight-based dosing approach did not appear to substantially influence the results of the economic model. The Committee also noted that the longer time horizon in the manufacturer's model compared with previous models did not dramatically affect the results, although it highlighted that a 40-year time horizon was preferable to ensure consistency with previous appraisals. During consultation, a manufacturer of a comparator drug noted that the withdrawal rate for ustekinumab had been taken from studies of TNF alpha inhibitors, and that it may be more appropriate to use the withdrawal rate from the PSUMMIT studies. The Committee heard from the manufacturer that the withdrawal rate in PSUMMIT 1 was lower than that included in the model. However, the Committee was also aware that this rate was derived from a study of 2 years' duration and the long-term withdrawal rate for ustekinumab is unknown, but the economic model had a lifetime horizon. The effect of this assumption on the model was not presented, but the Committee considered that if the withdrawal rate were lower than 16.5%, the ICERs for ustekinumab might be expected to decrease by a small amount. The Committee concluded that the weight-based dosing assumption, the time horizon and the withdrawal rate were not key drivers of the economic model and they did not have a substantial effect on the ICERs.

4.17 The Committee considered the appropriateness of appraising ustekinumab 45 mg alone, in light of the additional analyses presented by the manufacturer and the ERG. In considering the likely roles of the 45-mg and 90-mg doses, based on input from the clinical specialists the Committee considered that both doses were likely to be used in clinical practice (see section 4.10). Moreover, the Committee noted the evidence on which the conclusions of the EMA and the marketing authorisation were based, and considered that there was an indication that ustekinumab may be more effective at the higher dose, particularly for people weighing more than 100 kg. The Committee also

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considered in detail whether appraising ustekinumab 45 mg alone might have the potential to lead to unfair or discriminatory recommendations, if the higher dose were more effective in people weighing more than 100 kg. The Committee concluded that, based on the likely use of ustekinumab in clinical practice and the potential for effectiveness differences between the doses (particularly in people weighing more than 100 kg), it would not be appropriate for it to consider ustekinumab 45 mg alone.

4.18 The Committee considered the cost effectiveness of ustekinumab in the TNF alpha inhibitor-naive population. The Committee considered the incremental analysis to be appropriate for most people with psoriatic arthritis, for whom TNF alpha inhibitors are the most appropriate comparator (see section 4.3). The Committee noted the manufacturer's correction to the model submitted during consultation, and considered it appropriate. It noted that in the manufacturer's and ERG's base-case incremental analyses and all incremental scenario analyses, ustekinumab was dominated by (that is, was more expensive and less effective than) adalimumab: in the manufacturer's base case (final model, probabilistic analysis) ustekinumab was associated with additional costs of £5800, but 0.19 fewer QALYs, compared with adalimumab (see section 3.12). Moreover, the Committee noted that the cost-effectiveness analyses were subject to uncertainty because of the potential impact of incorporating the preferred assumptions relating to the assessment of treatment response at the same time for ustekinumab and conventional management, the effect of conventional management on skin symptoms, and the potential increase in HAQ-DI during ustekinumab treatment; all of these would be expected to reduce the cost effectiveness of ustekinumab. The Committee therefore concluded that ustekinumab is not a cost-effective option for treating psoriatic arthritis in people who have not previously received TNF alpha inhibitors compared with TNF alpha inhibitors.

4.19 The Committee also considered the cost effectiveness of ustekinumab in people who have not previously received TNF alpha inhibitors and for whom TNF alpha inhibitors are inappropriate because of contraindications. In this population, the Committee considered that conventional management is the most appropriate comparator. It emphasised that ustekinumab is innovative for this population, as it potentially fulfils an important unmet need. It noted that

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the number of people in this situation was unknown and may be very small, although it was aware of the need to identify subgroups for whom the technology may be cost effective. Moreover, the Committee noted that no evidence had been presented specifically for this population; the available evidence was drawn from the PSUMMIT studies, which were likely to have included a mixture of people for whom TNF alpha inhibitors would and would not be appropriate. The Committee considered that the most plausible ICER for ustekinumab compared with conventional management was likely to be more than £30,000 per quality-adjusted life year (QALY) gained: the manufacturer and ERG presented base-case ICERs between £23,000 and £24,000 per QALY gained (see sections 3.12 and 3.23), and incorporating the Committee's preferred assumptions would increase the ICER by more than £7000 per QALY gained (see below). In particular, assessing treatment response at week 24 for both ustekinumab and conventional management increased the ICER by approximately £6800–7000 per QALY gained (in the manufacturer's and ERG's analyses; see sections 3.14 and 3.23), The Committee also noted that incorporating the effect of conventional management on skin symptoms and the potential increase in HAQ-DI during ustekinumab treatment would both increase the ICER further (see sections 4.12 and 4.13). The Committee concluded that although the most plausible ICER was subject to considerable uncertainty, it was confident that the ICER would be higher than £30,000 per QALY gained. Although there is considerable unmet need in this population, the Committee considered that it would not be reasonable to recommend ustekinumab in this group, given the high ICER and in light of the treatments that would be displaced elsewhere in the NHS if ustekinumab was recommended. The Committee therefore could not recommend ustekinumab as a cost-effective use of NHS resources in people who have not previously received TNF alpha inhibitors and for whom TNF alpha inhibitors are inappropriate because of contraindications.

4.20 The Committee considered the cost effectiveness of ustekinumab in the TNF alpha inhibitor-exposed population. It noted that for most people an alternative TNF alpha inhibitor is the most appropriate comparator, which was not presented in the manufacturer's submission. The Committee therefore considered the exploratory sequencing analysis presented by the ERG. This analysis assessed the cost effectiveness of ustekinumab and TNF alpha

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inhibitors when used as second-line treatments, when first-line treatment with a TNF alpha inhibitor had failed because of lack of efficacy or adverse reactions. The ERG and the Committee acknowledged that this analysis is subject to considerable uncertainty, particularly because there was no distinction between people whose disease showed no initial response to TNF alpha inhibitors and those for whom TNF alpha inhibitors failed during long-term treatment; the clinical specialists noted that these groups represent 2 distinct populations. Nevertheless, the Committee considered that this exploratory analysis provided useful information for establishing a full picture of the cost effectiveness of ustekinumab. The Committee considered that the most informative scenario was the one in which the first-line TNF alpha inhibitor failed because of lack of efficacy and clinical effectiveness data for ustekinumab were taken directly from PSUMMIT 2, and noted that this analysis was the most favourable for ustekinumab. It noted that in this scenario the ICER for ustekinumab ranged from £32,800 to £37,700 per QALY gained, compared with adalimumab and etanercept respectively. The Committee acknowledged that the cost effectiveness of ustekinumab compared with TNF alpha inhibitors in this population was subject to considerable uncertainty. It understood that, even in the most favourable scenario presented by the ERG, ustekinumab was associated with ICERs exceeding £30,000 per QALY gained. The Committee therefore concluded that the best available evidence suggests that ustekinumab is not cost effective compared with TNF alpha inhibitors for treating psoriatic arthritis in people who have previously received TNF alpha inhibitors and for whom treatment with a subsequent TNF alpha inhibitor is appropriate.

4.21 The Committee considered the cost effectiveness of ustekinumab in the TNF alpha inhibitor-exposed population, looking specifically at people for whom TNF alpha inhibitors as a class had failed. It understood the important unmet need for people in this situation. The Committee also understood that there is limited evidence for this population, because the PSUMMIT 2 study included a mixture of people for whom subsequent TNF alpha inhibitors would and would not be appropriate. It highlighted that conventional management is an appropriate comparator in this population. The Committee considered that the most plausible ICER for ustekinumab compared with conventional management in the TNF alpha inhibitor-exposed population was likely to be

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more than £38,000 per QALY gained: the manufacturer's base-case ICER was £29,100 per QALY gained (see section 3.13), and incorporating the Committee's preferred assumptions would increase the ICER by more than £9000 per QALY gained. The Committee noted that most of the scenarios explored by the manufacturer and the ERG increased the ICER, and in particular, assessing treatment response at week 24 for both ustekinumab and conventional management increased the ICER by approximately £9400 per QALY gained. Furthermore, incorporating the effect of conventional management on skin symptoms and the potential increase in HAQ-DI during ustekinumab treatment (see section 4.19) were both likely to increase the ICER further, although the size of this effect was unknown. The Committee concluded that the most plausible ICER for ustekinumab compared with conventional management was considerably more than £30,000 per QALY gained. Consequently, the Committee concluded that although there was considerable unmet need, it would not be reasonable to recommend ustekinumab as a cost-effective use of NHS resources for people with psoriatic arthritis who have previously received TNF alpha inhibitor treatment and for whom TNF alpha inhibitors as a class had failed, given the high ICER and in light of the treatments that would be displaced elsewhere in the NHS if ustekinumab was recommended.

4.22 The Committee considered evidence from the manufacturer on the innovative nature of ustekinumab. It heard from the clinical specialists that they considered ustekinumab to be an innovative technology, because it is in a different class to the TNF alpha inhibitors and targets a different inflammatory pathway. They considered ustekinumab to be a particularly valuable treatment option in people for whom TNF alpha inhibitors are not appropriate, and the Committee noted that there may be an important unmet need in people for whom TNF alpha inhibitors are inappropriate or not effective. However, the Committee considered that although the introduction of TNF alpha inhibitors represented a 'step change' in managing psoriatic arthritis, evidence from the mixed treatment comparison suggested that ustekinumab may be less effective than TNF alpha inhibitors and so ustekinumab does not represent a clear-cut further step change compared with TNF alpha inhibitors. The Committee also considered the innovative nature of ustekinumab for people for whom TNF alpha inhibitors are inappropriate. It understood that some of the

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contraindications for TNF alpha inhibitors also apply to ustekinumab, so ustekinumab would not be appropriate for all people for whom TNF alpha inhibitors are unsuitable. The Committee considered that all of the health-related benefits associated with ustekinumab had been adequately captured in the economic model, and no changes to the recommendations were needed for that reason. Furthermore, the Committee considered that although ustekinumab is innovative for people for whom TNF alpha inhibitors are inappropriate (for whom there is considerable unmet need), the ICERs for ustekinumab compared with conventional management were high. The Committee therefore concluded that, being aware of the treatments that would be displaced if ustekinumab were recommended, it would not be reasonable to recommend ustekinumab in this population.

4.23 The patient expert highlighted that people with psoriatic arthritis often have concerns about the long-term safety of treatments for this condition. The Committee was aware of registers that collect evidence on the long-term treatment outcomes with TNF alpha inhibitors for rheumatoid arthritis and psoriasis. The patient expert and clinical specialists emphasised the importance of collecting long-term data on psoriatic arthritis specifically. The Committee concluded that long-term evidence on the effectiveness and safety of biological treatments for psoriatic arthritis would be valuable.

Summary of Appraisal Committee's key conclusions

TA313	**Appraisal title: Ustekinumab for treating active psoriatic arthritis**	**Section**
Key conclusion		
Ustekinumab is not recommended within its marketing authorisation for treating active psoriatic arthritis, that is, alone or in combination with methotrexate in adults when the response to previous non-biological disease-modifying antirheumatic drug (DMARD) therapy has been inadequate.		1.1

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The Committee concluded that ustekinumab is clinically effective compared with conventional management, in both tumour necrosis factor (TNF) alpha inhibitor-naive and TNF alpha inhibitor-exposed populations. However, based on evidence from the manufacturer's mixed treatment comparison, it concluded that ustekinumab appeared to be less effective than TNF alpha inhibitors for Psoriasis Area and Severity Index (PASI) 75, PASI90 and Psoriatic Arthritis Response Criteria (PsARC) response rates, particularly for the joint outcome. The Committee concluded that ustekinumab could not be recommended as a cost-effective use of NHS resources.	4.6 and 4.8
• In people who have not previously received TNF alpha inhibitors, ustekinumab was dominated by (that is, was more expensive and less effective than) adalimumab.	4.18
• In people who have not previously received TNF alpha inhibitors and for whom TNF alpha inhibitors are inappropriate, the most plausible incremental cost effectiveness ratio (ICER) for ustekinumab compared with conventional management was more than £30,000 per quality adjusted life year (QALY) gained. If the model also incorporated the effect of conventional management on skin symptoms and the potential increase in HAQ-DI during ustekinumab treatment, the ICER would increase further.	4.19
• In people who have previously received TNF alpha inhibitors, the cost effectiveness of ustekinumab compared with TNF alpha inhibitors is uncertain; even in the most favourable scenario for ustekinumab, it was associated with ICERs exceeding £30,000 per QALY gained.	4.20
• In people who have previously received TNF alpha inhibitors and for whom TNF alpha inhibitors as a class have failed, the most plausible ICER for ustekinumab compared with conventional management was considerably more than £30,000 per QALY gained. If the model also incorporated the effect of conventional management on skin symptoms and the potential increase in HAQ-DI during ustekinumab treatment, the ICER would increase further.	4.21
Current practice	

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Clinical need of patients, including the availability of alternative treatments	The Committee heard from patients and clinical specialists that TNF alpha inhibitors are the only class of treatments with robustly demonstrated efficacy, because conventional management with DMARDs, such as methotrexate, does not appear to provide substantial benefits for joint-related aspects of psoriatic arthritis.	4.2
	The Committee heard from the clinical specialists that there is a group of people with psoriatic arthritis for whom TNF alpha inhibitors are not suitable, because of contraindications such as heart failure or demyelination or because of failure of TNF alpha inhibitors as a class. For these people there is a considerable unmet need.	4.4
	The Committee understood that psoriatic arthritis is a lifelong condition that has a serious impact on people's quality of life.	4.5
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Clinical specialists considered ustekinumab to be a particularly valuable treatment option in people for whom TNF alpha inhibitors are not appropriate, and the Committee noted that there may be an important unmet need in people for whom TNF alpha inhibitors are inappropriate or not effective.	4.22
	The Committee considered that although the introduction of TNF alpha inhibitors represented a 'step change' in managing psoriatic arthritis, evidence from the mixed treatment comparison suggested that ustekinumab may be less effective than TNF alpha inhibitors and so ustekinumab does not represent a clear-cut further step change compared with TNF alpha inhibitors. The Committee considered that ustekinumab is innovative for people for whom TNF alpha inhibitors are inappropriate.	4.22
What is the position of the treatment in the pathway of care for the condition?	Ustekinumab has a UK marketing authorisation for use alone or in combination with methotrexate 'for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying antirheumatic drug (DMARD) therapy has been inadequate'.	2.1

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	Clinical trials of ustekinumab have been conducted in adults with active psoriatic arthritis despite current or previous treatment, including people who had previously received DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs) and/or TNF alpha.	3.1
	The Committee heard from clinical specialists that treatment of psoriatic arthritis follows current NICE guidance: after initial treatment with NSAIDs and DMARDs, most people will be treated with a TNF alpha inhibitor. The Committee noted that Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (NICE technology appraisal guidance 199) and Golimumab for the treatment of psoriatic arthritis (NICE technology appraisal guidance 220) recommend TNF alpha inhibitor therapy for people with psoriatic arthritis, and also recommend that treatment should normally be started with the least expensive drug (taking into account administration costs, required dose and price per dose).	4.2
	The Committee heard from clinical specialists that if ustekinumab were to be used in people with prior TNF alpha inhibitor exposure, it might be used after 1, 2 or more TNF alpha inhibitors, depending on person-specific factors.	4.3
	The Committee concluded that the most appropriate comparators for ustekinumab in most people with psoriatic arthritis would be TNF alpha inhibitors, both in people who have not received prior TNF alpha inhibitors and in those who have previously received TNF alpha inhibitor therapy. It also concluded that conventional management would be an appropriate comparator in people in whom TNF alpha inhibitors were contraindicated and in people whose condition failed to respond to TNF alpha inhibitors as a class.	4.3 and 4.4

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Adverse reactions	The manufacturer presented adverse event data from the PSUMMIT studies, 5-year extensions of 4 studies of ustekinumab in psoriasis, the Psoriasis Longitudinal Assessment and Registry (PSOLAR) and the British Society for Rheumatology Biologics Register (BSRBR). The incidence of adverse events in the PSUMMIT studies was similar in the ustekinumab treatment arms compared with the placebo arms.	3.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the evidence for the clinical effectiveness of ustekinumab had been taken from 2 randomised placebo-controlled trials (PSUMMIT 1 and 2).	4.6
	The Committee concluded that ustekinumab is clinically effective compared with conventional management, in both TNF alpha inhibitor-naive and TNF alpha inhibitor-exposed populations, but acknowledged that there remains some uncertainty about the long-term effects of ustekinumab.	4.6
	The Committee considered the clinical effectiveness of ustekinumab compared with TNF alpha inhibitors in the TNF alpha inhibitor-naive population. The Committee reviewed the findings of the manufacturer's mixed treatment comparison and discussed them with the clinical specialists, and was aware of the limitations of the mixed treatment comparison. It concluded that ustekinumab appeared to be less effective than TNF alpha inhibitors for PASI75, PASI90 and PsARC response, particularly for the joint outcome.	4.8
Relevance to general clinical practice in the NHS	People in the PSUMMIT 1 and 2 trials generally had long-standing moderate to severe active psoriatic arthritis with impaired physical function and high numbers of tender and swollen joints. In both PSUMMIT 1 and 2, approximately 70% of patients had skin disease, and 80–90% of patients had received prior DMARD therapy.	3.1

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Uncertainties generated by the evidence	The Committee considered that although the effect of ustekinumab is likely to persist for up to 1 year, there is some uncertainty about this because in the trials people switched from placebo to ustekinumab at week 24.	4.6
	It considered that the evidence on radiographic progression with ustekinumab must be interpreted with caution.	4.7
	It also acknowledged that there remains some uncertainty about the long-term effects of ustekinumab.	4.6
	The Committee was aware of the limitations of the mixed treatment comparison.	4.8
	The Committee concluded that there is still uncertainty about the relative effectiveness of ustekinumab and TNF alpha inhibitors in people who have previously received TNF alpha inhibitors.	4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee considered the clinical effectiveness of ustekinumab compared with TNF alpha inhibitors in the TNF alpha inhibitor-naive population. It was not persuaded that a clinical benefit was shown for ustekinumab compared with TNF alpha inhibitors in the TNF alpha inhibitor-naive population, based on the available evidence. It concluded that ustekinumab appeared to be less effective than TNF alpha inhibitors for PASI75, PASI90 and PsARC response, particularly for the joint outcome.	4.8
	The Committee also considered the clinical effectiveness of ustekinumab compared with TNF alpha inhibitors in the TNF alpha inhibitor-exposed population. The Committee was aware that there is no clinical trial evidence from which to compare ustekinumab and TNF alpha inhibitors. Evidence presented at a recent conference suggested that the effectiveness of ustekinumab measured using the American College of Rheumatology (ACR) criteria may decrease with increasing numbers of prior TNF alpha inhibitors.	4.9
	The Committee concluded that there is still uncertainty about the relative effectiveness of ustekinumab and TNF alpha inhibitors in people who have previously received TNF alpha inhibitors.	4.9

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	The Committee also considered whether there may be any variation in clinical effectiveness depending on the reason for withdrawal of the first TNF alpha inhibitor but it acknowledged that there was not enough evidence for this aspect to be considered further.	4.9
	The Committee concluded that there is no clear evidence to support the use of a strict weight-based dosing strategy.	4.10
	The Committee considered that there was an indication that ustekinumab may be more effective at the higher dose, particularly for people weighing more than 100 kg.	4.17
Estimate of the size of the clinical effectiveness including strength of supporting evidence	In both PSUMMIT 1 and 2, ustekinumab was associated with statistically significantly higher rates of ACR20 response at week 24 than placebo. ACR20 response rates in PSUMMIT 1 were 46.0% and 22.8% for ustekinumab 45 mg and 90 mg pooled and placebo respectively ($p<0.0001$).	3.3
	The Committee concluded that ustekinumab is clinically effective compared with conventional management, in both TNF alpha inhibitor-naive and TNF alpha inhibitor-exposed populations, but acknowledged that there remains some uncertainty about the long-term effects of ustekinumab.	4.6
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer's economic model comprised a short-term decision tree followed by a long-term Markov model with a lifetime (52-year) time horizon. It was similar to the models used in previous NICE appraisals of treatments for psoriatic arthritis.	3.9
	The Committee considered the structure, assumptions and results in the manufacturer's economic model and the critique presented by the Evidence Review Group (ERG).	4.11

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Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee discussed key assumptions about the improvement, rebound and progression of joint symptoms, the effect of conventional management on skin symptoms, the use of the utility equation, the timing of the assessment of response and the sequencing of biological treatments in the TNF alpha inhibitor-exposed population.	4.11
	The Committee concluded that there remains considerable uncertainty as to how well the Health Assessment Questionnaire Disability Index (HAQ-DI) assumptions apply to ustekinumab, but considered that the assumptions in the model were a sufficient basis on which to make a decision	4.12
	The Committee considered the way in which the effect of conventional management on skin symptoms had been modelled. It considered that the manufacturer's model had underestimated the clinical benefits of conventional management and so had underestimated the ICER associated with ustekinumab compared with conventional management. It also noted that the size of the effect on the ICER is unknown.	4.13
	The Committee considered that all health-related quality of life evidence from the clinical trials – including the SF-36 data – should ideally be used if possible. However, because of the uncertainty in the newer utility equation, it concluded that using the previously published equation would be more appropriate.	4.14
	The Committee concluded that for pairwise comparisons between ustekinumab and conventional management, the treatment response should have been assessed at the same time point. The Committee had a preference for assessing treatment response at 24 weeks for both ustekinumab (in line with its summary of product characteristics) and conventional management.	4.15

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Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The model captured health-related quality of life through joint symptoms, disability and skin symptoms (PsARC response, HAQ-DI score and PASI score). HAQ-DI and PASI scores were then mapped to EQ-5D using an equation used in previous NICE appraisals of psoriatic arthritis treatments.	3.11
	The Committee noted that the manufacturer's base-case analysis was based on utility scores derived using a previously published equation used in the appraisals of etanercept, infliximab and adalimumab (NICE technology appraisal guidance 199) and golimumab (NICE technology appraisal guidance 220) for the treatment of psoriatic arthritis.	4.14
	It also noted that health-related quality of life evidence had been captured directly in the PSUMMIT studies, through the 36-item Short-Form Health Survey (SF-36). The Committee considered that all health-related quality of life evidence from the clinical trials – including the SF-36 data – should ideally be used if possible. However, because of the uncertainty in the newer utility equation, and the fact that the effectiveness of ustekinumab in the PSUMMIT trials was captured through the HAQ-DI and PASI scores, the Committee concluded that using the previously published equation would be more appropriate.	4.14
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that ustekinumab is not a cost-effective option compared with TNF alpha inhibitors in people for whom TNF alpha inhibitors would be considered, for either the TNF alpha inhibitor-naive population or the TNF alpha inhibitor-exposed population.	4.18 and 4.20
	The Committee considered people for whom TNF alpha inhibitors are inappropriate. In this group, conventional management is an appropriate comparator. The Committee concluded that in both TNF alpha inhibitor-naive and TNF alpha inhibitor-exposed populations, the ICERs were likely to be greater than £30,000 per QALY gained.	4.19 and 4.21

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What are the key drivers of cost effectiveness?	Deterministic sensitivity analyses showed that the results were most sensitive to the change in HAQ-DI score over time associated with the natural history of psoriatic arthritis, the proportion of people who had a PsARC response, and the HAQ-DI change associated with PsARC response.	3.13 and 3.14
	In particular, the Committee discussed key assumptions about the improvement, rebound and progression of joint symptoms, the effect of conventional management on skin symptoms, the use of the utility equation, the timing of the assessment of response and the sequencing of biological treatments in the TNF alpha inhibitor-exposed population.	4.11
Most likely cost-effectiveness estimate (given as an ICER)	In the TNF alpha inhibitor-naive population ustekinumab was dominated by (that is, was more expensive and less effective than) adalimumab.	4.18
	In people who have not previously received TNF alpha inhibitors and for whom TNF alpha inhibitors are inappropriate because of contraindications, the Committee concluded that the most plausible ICER was likely to be more than £30,000 per QALY gained.	4.19
	In the TNF alpha inhibitor-exposed population, even in the most favourable scenario presented by the ERG, ustekinumab was associated with ICERs exceeding £30,000 per QALY gained compared with TNF alpha inhibitors.	4.20
	In the TNF alpha inhibitor-exposed population, looking specifically at people for whom TNF alpha inhibitors as a class had failed, the Committee concluded that the most plausible ICER for ustekinumab compared with conventional management was considerably more than £30,000 per QALY gained.	4.21
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	

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End-of-life considerations	Not applicable	
Equalities considerations and social value judgements	The Committee also considered in detail whether appraising ustekinumab 45 mg alone might have the potential to lead to unfair or discriminatory recommendations, if the higher dose were more effective in people weighing more than 100 kg. It concluded that, based on the likely use of ustekinumab in clinical practice and the potential for effectiveness differences between the doses (particularly in people weighing more than 100 kg), it would not be appropriate for it to consider ustekinumab 45 mg alone.	4.17

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5 Implementation

5.1 NICE has developed a costing statement explaining the resource impact of this guidance to help organisations put this guidance into practice.

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6 Recommendations for further research

6.1 The Committee considered that there is an important need for head-to-head comparisons between biological treatments for psoriatic arthritis, particularly in people for whom treatment with tumour necrosis factor (TNF) alpha inhibitors has been unsuccessful.

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7 Review of guidance

7.1 The guidance on this technology will be considered for review in May 2017. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
May 2014

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8 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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 Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
GP, West Coker Surgery, Somerset

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Andrew Black
GP, Mortimer Medical Practice, Herefordshire

Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

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Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital, Cardiff

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon
Professor of Health Economics, University of Sheffield

Dr Martin Duerden
Assistant Medical Director, Betsi Cadwaladr Health Board, North Wales

Susan Dutton
Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker
Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Gillian Ells
Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Professor John Henderson
Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Paul Hepple
General Practitioner, Muirhouse Medical Group

Professor John Hutton
Professor of Health Economics, University of York

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Professor Peter Jones
Emeritus Professor of Statistics, Keele University

Professor Steven Julious
Professor in Medical Statistics, University of Sheffield

Dr Tim Kinnaird
Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Emily Lam
Lay Member

Dr Warren Linley
Senior Medicines Commissioning Pharmacist, Staffordshire and Lancashire Commissioning Support Unit

Malcolm Oswald
Lay member

Dr Oluwafemi Oyebode
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford
Director of Public Health, Rotherham Primary Care Trust and MBC

Dr Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Peter Sims
GP, Devon

Dr Murray Smith
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Cliff Snelling
Lay Member

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NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ian Watson
Technical Lead

Eleanor Donegan
Technical Adviser

Kate Moore
Project Manager

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9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Centre for Reviews and Dissemination and Centre for Health Economics, University of York:

- Craig D, O'Connor J, Rodgers M et al. Ustekinumab for treating active and progressive psoriatic arthritis: a single technology appraisal, October 2013

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

II. Professional/specialist and patient/carer groups:

- Psoriasis and Psoriatic Arthritis Alliance
- Psoriasis Association
- British Association of Dermatologists
- British Society for Rheumatology
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England

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- Welsh Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- AbbVie
- Merck Sharp & Dohme
- Novartis Pharmaceuticals
- Pfizer
- Arthritis Research UK
- NHS Centre for Reviews and Dissemination and Centre for Health Economics, University of York
- National Institute for Health Research Health Technology Assessment Programme

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 by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Eleanor Korendowych, Consultant Rheumatologist, nominated by British Society for Rheumatology – clinical specialist
- Professor Dennis McGonagle, Professor of Investigative Rheumatology – clinical specialist, nominated by Janssen
- David Chandler, Chief Executive of the Psoriasis and Psoriatic Arthritis Alliance, nominated by Psoriasis and Psoriatic Arthritis Alliance – patient expert

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D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Janssen

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About this guidance

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

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

It has been incorporated into the NICE pathway on psoriasis in the systemic biological therapy for psoriasis and psoriatic arthritis path along with other related guidance and products.

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

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Your responsibility

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

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

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