Ustekinumab for treating active psoriatic arthritis

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

> This guidance replaces TA313.

1 Recommendations

1.1 Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:

- treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis) or

- the person has had treatment with 1 or more TNF–alpha inhibitors.

1.2 Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. As recommended in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, people whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see NICE's technology appraisal guidance on ustekinumab for the treatment of adults with moderate to severe psoriasis).

1.3 When using the Psoriatic Arthritis Response Criteria (PsARC) healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.

1.4 People whose treatment with ustekinumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published,

should be able to continue ustekinumab until they and their NHS clinician consider it appropriate to stop.

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 marketing authorisation in the UK 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 £2,147 per 45-mg vial (excluding VAT; BNF online [accessed February 2015]). 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 stopping treatment in people whose psoriatic arthritis has shown no response after up to 28 weeks of treatment. The average annual acquisition cost for ustekinumab 45 mg is £10,735 in the first year and £9,304 per year thereafter. The company has agreed a patient access scheme with the Department of Health, in which the company provides the 90-mg dose (2 vials) at the same cost as the 45-mg dose (1 vial), for people who weigh more than 100 kg and need the higher dose. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The patient access scheme was withdrawn in January 2017 because the company now provides a 90-mg vial at the same cost as the 45-mg vial.

3 The company's submission

The Appraisal Committee considered evidence submitted by Janssen as part of NICE technology appraisal guidance 313, further evidence submitted by Janssen as part of the rapid review and reviews of these submissions by the Evidence Review Group (ERG).

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 3 studies 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 had disease-modifying antirheumatic drugs (DMARDs) with or without non-steroidal anti-inflammatory drugs (NSAIDs) only, whereas PSUMMIT 2 (n=312) also included people who had previously had 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% to 90% of patients had received prior DMARD therapy. Of the 180 people in PSUMMIT 2 who had previously had TNF-alpha inhibitors (referred to in this document as 'TNF-alpha inhibitor-exposed'), more than half had received at least 2 biological 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 have 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 end point 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 end points included measures of joint symptoms (including modified Psoriatic Arthritis Response Criteria [PsARC] and ACR 50/70), 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 ACR 20 response at week 24 than placebo. ACR 20 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. ACR 20 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. ACR 20 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.

3.6   The results from secondary outcome analyses at week 24 generally supported the conclusions from the ACR 20 results. The findings were observed across joint, radiographic, skin, soft tissue and health-related quality-of-life end points, 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; PASI 75 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 PASI 75 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 company 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 had TNF-alpha inhibitors (referred to in this document as 'TNF-alpha inhibitor-naive'). The company 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, PASI 75 and PASI 90 responses to treatment at weeks 12 to 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 had ustekinumab 45 mg, and patients who weighed more than 100 kg had ustekinumab 90 mg. For the TNF-alpha inhibitors, data were taken directly from 7 randomised, double-blind, placebo-controlled studies carried out in people with active psoriatic arthritis. The company reported that the findings showed that ustekinumab and TNF-alpha inhibitors have better outcomes than placebo 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 company reported that in the analyses of skin symptoms, there may be higher probabilities of response with infliximab (PASI 75 and PASI 90), golimumab 100 mg (PASI 75) and adalimumab (PASI 90) compared with other biological drugs, although the credible intervals were overlapping.

3.8　The company presented adverse event data from the PSUMMIT studies, 5-year extensions of 4 studies of ustekinumab in psoriasis, the Psoriasis Longitudinal Assessment and Registry and the British Society for Rheumatology Biologics Register. 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%; and placebo, 47.9%. There were no disproportionate increases in adverse event rates over time. The most common adverse reactions seen 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

3.9　The company presented a de novo economic analysis that assessed the cost effectiveness of ustekinumab for treating adults with active psoriatic arthritis for whom the response to previous DMARD therapy has been inadequate. Ustekinumab was compared with TNF-alpha inhibitors and conventional management in people who were TNF-alpha inhibitor-naive, and with conventional management only in people who were TNF-alpha inhibitor-exposed.

The patient populations were based on the populations in the company's mixed treatment comparison and PSUMMIT 1 and 2. It was assumed that all patients who weigh less than 100 kg would have ustekinumab 45 mg, and all those who weigh more than 100 kg would have 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 (etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis). In the decision tree phase, people had initial biological therapy for either 12 weeks (TNF-alpha inhibitors) or 24 weeks (ustekinumab). At this point, people who had a PsARC response (defined as an improvement in at least 2 of the 4 criteria, 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria) continued with biological therapy, and those who did not switched to conventional management. All patients then entered the Markov phase of the model. People having a biological therapy continued to have 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.

3.10   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 at the time of the submission there were 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.

3.11   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 PASI score until withdrawal of active treatment. Throughout periods of conventional management, people's disease progressed according 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 NICE technology appraisal guidance for etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis. 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 given by subcutaneous injection at no cost to the NHS.

3.12   A number of iterations of the economic model were presented by the company: the first in its original submission (referred to in this document as the 'original' model), the second corrected after the clarification stage (referred to in this document as the 'post-clarification' model), and the third corrected during consultation (referred to in this document as the 'post-consultation' model). A further iteration, incorporating the patient access scheme and 1 amended assumption, was presented by the company in its submission for the rapid review of NICE technology appraisal guidance 313 (referred to in this document as the 'rapid review' model; see section 3.30). The original model was used to develop base-case, deterministic and probabilistic sensitivity analyses, and a series of scenario analyses; the results of the base-case and scenario analyses were replaced by the post-clarification and post-consultation models and so are not reported here. The post-clarification 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 company used this model to develop an updated base case and updated scenario analyses. The post-consultation model submitted during consultation corrected an error, identified by the company and a consultee 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 post-consultation model, which replaced the previous models. The cost-effectiveness evidence presented here for the TNF-alpha inhibitor-exposed population is based on the post-clarification model (because the TNF-alpha inhibitors were not included as comparators in this population, and therefore the golimumab error did not apply).

3.13 In the TNF-alpha inhibitor-naive population (post-consultation model, probabilistic results), ustekinumab was associated with total costs of £70,249 and a total of 6.23 quality-adjusted life years (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 company also presented pairwise comparisons between ustekinumab and conventional management (post-consultation 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.

3.14 In the TNF-alpha inhibitor-exposed population (post-clarification 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.

3.15 The company presented a series of scenario analyses for both the TNF-alpha

inhibitor-naive and -exposed populations (post-clarification model). These 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 showed 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.

Evidence Review Group's critique and exploratory analyses of the company's submission

3.16 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 had TNF-alpha inhibitors, and that treatment effects were not statistically significantly different between ustekinumab doses.

3.17 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 had varying numbers of TNF-alpha inhibitors for varying durations. The ERG emphasised that the analyses of PSUMMIT 2 did not distinguish between people who had previously had 1, 2, 3 or more TNF-alpha inhibitors, and so did not differentiate between people who had tried only some of the available TNF-alpha inhibitors and 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, making interpretation of the results difficult.

3.18   The ERG considered that, despite some heterogeneity between trials, the mixed treatment comparison was appropriate to carry out 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 PASI 75, PASI 90 and PsARC.

3.19   The ERG noted that the company's economic model was similar to those used in previous NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis, although it had a longer time horizon (52 years compared with 40 years). The ERG 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.

3.20   The ERG highlighted weaknesses in the clinical effectiveness parameters used in

the model. It noted that the company 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 3.24 and 3.25). Furthermore, the ERG queried the model assumption that people having conventional management did not have any improvement in PASI, whereas in clinical practice skin symptoms often respond well to DMARDs.

3.21 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 have subsequent biological therapies. Thus, the costs and benefits associated with subsequent lines of biological treatment were not included in the model. The ERG stated that 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.

3.22 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.

3.23 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 company 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 between people who had tried only some of the available TNF-alpha inhibitors and people for whom TNF-alpha inhibitors as a class had failed. The ERG stated that, 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 company'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 had 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.

3.24   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 company'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 showed that, in the incremental analysis (comparing ustekinumab, TNF-alpha inhibitors and conventional management), ustekinumab remained dominated in all modelled scenarios. Probabilistic ICERs for ustekinumab compared with conventional management ranged from £22,455 to £55,029 per QALY gained. In particular, the ERG's analyses showed that assessing the response to treatment at week 24 for both ustekinumab and conventional management increased the ICER by £6,987 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 company's post-clarification 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 NICE's technology appraisal guidance on golimumab for the treatment of psoriatic arthritis. In this analysis, ustekinumab was dominated by adalimumab. Compared with conventional 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.

3.25   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 carried out 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.

Company's additional analyses provided during consultation and Evidence Review Group's critique

3.26   In response to consultation, the company submitted additional evidence exploring the cost effectiveness of the 45-mg dose of ustekinumab alone, based on the post-consultation model. The company noted that ustekinumab 45 mg could potentially be considered for all patients. In the base-case analysis for the TNF-alpha inhibitor-naive population, ustekinumab 45 mg was the lowest-cost and least effective biological treatment. In the TNF-alpha inhibitor-exposed population (base case, probabilistic analysis), ustekinumab 45 mg was associated with an ICER of £21,789 per QALY gained compared with conventional management. The company also reproduced the ERG's exploratory sequencing analysis and presented scenario analyses to explore the impact of key assumptions.

3.27   The ERG submitted a critique of these analyses. It noted that, in principle, the scenario in which all patients have ustekinumab 45 mg is reasonable to explore, but highlighted that there is uncertainty about the validity of this scenario in clinical practice. The ERG applied the 45-mg dosing assumption to its preferred base case for the TNF-alpha inhibitor-naive population (see section 3.24), and noted that the results were generally similar to those presented by the company. For the TNF-alpha inhibitor-exposed population, the ERG confirmed that the company had correctly reproduced its exploratory sequencing analysis, although it emphasised that this analysis was highly uncertain because it was based on numerous assumptions.

Further evidence

3.28   Based on a comment received during consultation from a company that manufactures 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), showing that ustekinumab inhibited radiographic progression compared with placebo and that this inhibition continued to week 52. Data from PSUMMIT 1 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 company 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 showed 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 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 NICE technology appraisal guidance

313 was prepared.

Rapid review of NICE technology appraisal guidance 313: patient access scheme

3.29   In NICE technology appraisal guidance 313, ustekinumab was not recommended for treating active psoriatic arthritis. After publication, the company agreed a patient access scheme with the Department of Health (see section 2.3) and submitted revised analyses to be considered in a rapid review of the guidance. Under the original patient access scheme the company provided 2x45 mg pre-filled syringes, for patients who needed the higher dose of 90 mg, at the same total cost to the NHS as for a single 45-mg pre-filled syringe. The patient access scheme was withdrawn in January 2017 because the company now provides a 90-mg vial at the same cost as the 45-mg vial.

3.30   The company submitted a revised economic analysis (the 'rapid review' model) based on its post-consultation model, incorporating the patient access scheme and an altered assumption about the effect of conventional management on skin symptoms (based on the Committee's considerations in NICE technology appraisal guidance 313). It presented analyses for both the TNF-alpha inhibitor-naive and -exposed populations. For the TNF-alpha inhibitor-exposed population, the company also presented a sequencing analysis. This analysis was developed from the ERG's exploratory sequencing analysis (see section 3.25) and used the scenario in which the first TNF-alpha inhibitor failed because of lack of efficacy and clinical effectiveness data were taken from the PSUMMIT 2 study. The company considered that including the patient access scheme considerably improved the cost effectiveness of ustekinumab.

3.31   The patient access scheme was incorporated by reducing the unit cost of ustekinumab 90 mg to £2,147. The company estimated the additional costs associated with the patient access scheme to be £33 per patient. It considered that these costs were very small and so would not affect the appraisal; therefore, it did not include them in the economic analyses.

3.32   The company modelled the effect of conventional management on skin

symptoms in the same way as it had modelled the effects of biological drugs in the original model – that is, assuming a fixed improvement in PASI score based on PASI response. As part of this change, the company also amended the rebound assumption for people who withdraw from biological therapy, such that the PASI score rebounded to a score based on the effect of conventional management (rather than the baseline score). The PASI scores and response rates for conventional management were taken from the placebo arms of the company's mixed treatment comparison and the PSUMMIT 1 and 2 studies.

3.33   In the company's base case for the TNF-alpha inhibitor-naive population (rapid review model, probabilistic results, incremental analysis), conventional management was the lowest cost option, followed by ustekinumab then adalimumab. Ustekinumab was therefore the least costly biological drug, and was associated with total costs of £59,105, a total of 6.09 QALYs and an ICER compared with conventional management of £23,164 per QALY gained. Adalimumab had a pairwise ICER compared with conventional management of £21,765 per QALY gained.

3.34   In the company's base case for the TNF-alpha inhibitor-exposed population (rapid review model, probabilistic results), ustekinumab was associated with total costs of £62,724 and a total of 4.08 QALYs. It was associated with an ICER of £25,675 per QALY gained, compared with conventional management. In the sequencing analysis, ustekinumab was associated with deterministic ICERs ranging from £21,241 per QALY gained (compared with etanercept, when adalimumab, golimumab or infliximab are used first line) to £25,921 per QALY gained (compared with conventional management, when etanercept is used first line).

3.35   For both the TNF-alpha inhibitor-naive and exposed populations, the company presented a deterministic sensitivity analysis and scenario analyses consistent with those it presented in the original submission. In both populations, the results were most sensitive to the change in HAQ-DI score over time associated with the natural history of psoriatic arthritis. In scenarios based on the TNF-alpha inhibitor-naive population, ustekinumab was associated with deterministic ICERs compared with conventional management of £21,411 to £29,580 per QALY gained. In equivalent scenarios based on the TNF-alpha inhibitor-exposed population, ustekinumab was associated with deterministic ICERs compared with

conventional management of £23,229 to £33,578 per QALY gained. In scenarios in which the response to all treatments was assessed at week 24, ustekinumab was associated with ICERs of £27,914 per QALY gained (TNF-alpha inhibitor-naive population) and £32,608 per QALY gained (TNF-alpha inhibitor-exposed population), compared with conventional management.

Evidence Review Group critique of the company's rapid review submission

3.36   The ERG noted that the company had appropriately incorporated the patient access scheme into the latest version of the economic model from NICE technology appraisal guidance 313 (the post-consultation model). It agreed with the company that the additional costs associated with the patient access scheme did not significantly alter the cost effectiveness of ustekinumab.

3.37   The ERG highlighted that, in the company's model for the TNF-alpha inhibitor-naive population, ustekinumab was extendedly dominated in all scenarios. An intervention is 'extendedly dominated' when it is more costly and less effective than a combination of 2 comparators; that is, the ICER for the intervention is higher than that of the next more effective comparator when both are compared with another less effective comparator. In the base case, ustekinumab was extendedly dominated by adalimumab and conventional management, because the ICER for ustekinumab compared with conventional management was higher than that of adalimumab compared with conventional management.

3.38   The ERG commented on the company's inclusion of the effect of conventional management on skin symptoms. It considered that the company's approach was mostly reasonable. However, the ERG highlighted that the PASI score to which people were assumed to rebound when they stop biological treatment was not the same as the average PASI score for people having conventional management. It noted that this difference resulted from differences in PASI response rates between week 12 (as applied to the conventional management arm) and week 24 (as applied to the biological therapy arms). The ERG commented that the effect of this assumption differed between the TNF-alpha inhibitor-naive and TNF-alpha

inhibitor-exposed populations.

3.39   The ERG identified a number of errors in the company's economic model, relating to disease-related costs, medical resource use, the accrual of QALYs in the second year of the model and the application of discounting. It noted that the errors tended to underestimate the costs and QALYs associated with psoriatic arthritis, and hence tended to underestimate the cost effectiveness of more effective treatments. Consequently, the ERG noted that correcting these errors caused the cost effectiveness of ustekinumab to improve relative to conventional management, but worsen relative to TNF-alpha inhibitors.

3.40   The ERG presented a scenario analysis to explore the patient access scheme combined with the Committee's preferred assumptions from NICE technology appraisal guidance 313. This analysis was developed from the company's rapid review model with the errors corrected, a 40-year time horizon and with the response to both ustekinumab and conventional management assessed at week 24. In this scenario (probabilistic analysis), in the TNF-alpha inhibitor-naive population ustekinumab remained extendedly dominated (by a combination of conventional management and adalimumab) and had an ICER of £21,857 per QALY gained compared with conventional management. In the TNF-alpha inhibitor-exposed population (probabilistic analysis), the ICER for ustekinumab was £25,292 per QALY gained, compared with conventional management. In the sequencing analysis based on this scenario, ustekinumab was associated with an ICER of £25,393 per QALY gained compared with conventional management, when golimumab, adalimumab or etanercept are used first line. The ERG noted that the time horizon had a small effect on the ICER, whereas the effect of the week-24 assessment time point was larger.

3.41   Full details of all the evidence are in the committee papers.

4 Consideration of the evidence

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 experts. It also took into account the effective use of NHS resources.

4.1   The Committee considered the current treatment pathway for people with psoriatic arthritis. It heard from the clinical experts 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 have treatment with a tumour necrosis factor (TNF) alpha inhibitor. The Committee heard from the clinical experts and a patient expert 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 NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis 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. The Committee heard from the clinical experts 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 experts 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 experts and the patient expert 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 on 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.

4.2   The Committee considered the likely place of ustekinumab in managing psoriatic arthritis. It heard from the clinical experts 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 had prior TNF-alpha inhibitors (referred to in this document as 'TNF-alpha inhibitor-naive') and in those who have previously had TNF-alpha inhibitor therapy (referred to in this document as 'TNF-alpha inhibitor-exposed').

4.3   The Committee heard from the clinical experts 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. The Committee understood that this affects a number of people and that for people in this situation there are no effective treatment options. The clinical experts 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 company that manufactures a TNF-alpha inhibitor that the contraindications for ustekinumab and TNF-alpha inhibitors are relatively similar. It therefore considered that the number of people who had not had 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 for whom TNF-alpha inhibitors were contraindicated and in people whose condition failed to respond to TNF-alpha inhibitors as a class.

4.4   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

4.5   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 the clinical experts that 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.

4.6   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 (in NICE's technology appraisal guidance on golimumab for the treatment of psoriatic arthritis) 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 company that interpretation of these findings was subject to 4 key difficulties:

- Changes in radiographic score were very small.

- The individual studies were not powered for this end point.

- There was a high level of missing data in the placebo arm because of patient withdrawal (approximately 23%).

- 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 should 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 company's economic

model (see section 4.11).

4.7   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 company'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, PASI 90 and PsARC response rates). It discussed this analysis with the clinical experts, 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 PASI 75, PASI 90 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. It was aware that there was limited clinical trial evidence in this setting. It understood from comments received during consultation that there is some evidence for the effectiveness of TNF-alpha inhibitors in the TNF-alpha inhibitor-exposed population, but was aware that there was not enough evidence to compare ustekinumab and TNF-alpha inhibitors. The Committee therefore 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 experts that evidence presented at a 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 experts 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. The Committee heard from the clinical experts 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%. Conversely, the Committee noted comments received during consultation from a company that manufactures a comparator drug (including evidence from a randomised controlled trial of certolizumab pegol and open-label

and observation studies of adalimumab) that 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 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 had TNF-alpha inhibitors.

4.9 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. It 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 have ustekinumab 90 mg, compared with people who weigh less than 100 kg and have ustekinumab 45 mg. Moreover, the EMA noted that the efficacy of ustekinumab 90 mg (in terms of ACR 20 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 company that the dose–response effect based on weight for psoriatic arthritis may not be as strong as seen in psoriasis and that the differences between doses were not statistically significant. The Committee also considered evidence from the Evidence Review Group (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 the clinical experts that if ustekinumab were recommended, they would anticipate using both the 45-mg and 90-mg doses in clinical practice (rather than only 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.

Cost effectiveness

4.10   The Committee considered the structure, assumptions and results in the
company's economic model and the critique presented by the 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. It then reviewed the effect of these assumptions on the
cost-effectiveness estimates for ustekinumab. The Committee also considered
the additional analyses incorporating the patient access scheme, presented
during the rapid review.

4.11   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 company's model (in which 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 3.11]) was consistent with the models used in previous
NICE technology appraisal guidance on TNF-alpha inhibitors for psoriatic arthritis
(etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and
golimumab for the treatment of psoriatic arthritis). It heard from the clinical
experts that HAQ-DI is an acceptable and sensitive treatment outcome measure.
The clinical experts 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 have 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 to 100 weeks that did not suggest a substantial worsening over time (see section 3.28; long-term analyses of HAQ-DI scores in PSUMMIT 2 were not available at the time NICE technology appraisal guidance 313 was prepared). The Committee 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 uncertainty remains 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.

4.12   The Committee considered the way in which the effect of conventional management on skin symptoms had been modelled. It noted that the company's original, post-clarification and post-consultation models (see section 3.12) assumed that conventional management strategies did not affect skin symptoms, but heard that the ERG's clinical adviser stated that in practice, DMARDs such as methotrexate often improve psoriasis symptoms. During consultation the Committee received additional information, from a company that manufactures a comparator drug, on the effect of conventional management on skin symptoms, taken from a study of adalimumab. In the rapid review, the Committee noted that the company updated its model to incorporate the effect of conventional management on skin symptoms. It heard from the ERG that the modelling approach was consistent with the approach taken for biological treatments in the original model, and understood that the ERG considered this mostly reasonable. The Committee concluded that it was appropriate to include the effect of conventional management on skin symptoms in the economic model.

4.13   The Committee noted that the company's base-case analysis was based on utility scores derived using a previously published equation used in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis. However, 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 understood that the company 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.

4.14   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 experts that there is some uncertainty about when ustekinumab begins to take effect, although its onset of action may be slower than TNF-alpha inhibitors. The clinical experts 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 experts 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 ideally 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. However, it understood that the company considered that there was no intrinsic reason why the timing of the assessment for ustekinumab and conventional management in the economic model must be the same, and that assessing the response to conventional management at 24 weeks would be inconsistent with NICE's technology appraisal

guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis. The Committee noted that assessing the response to conventional management at week 24 rather than week 12 increased the incremental cost-effectiveness ratio (ICER) for ustekinumab.

4.15   The Committee considered the impact of sensitivity analyses and scenario analyses on the results of the economic model. It noted that the company and the ERG presented a number of analyses (see sections 3.12, 3.24, 3.30 and 3.40). The Committee noted that the model was highly sensitive to assumptions about the HAQ-DI score. In addition to the key assumptions explored in sections 4.11 to 4.14, 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 company'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 company'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 consultee 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 company 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 time 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.

4.16   The Committee considered the appropriateness of appraising ustekinumab 45 mg alone, in light of the additional analyses presented by the company and the ERG (see sections 3.26 and 3.27). Based on input from the clinical experts, the Committee considered that both the 45-mg and 90-mg doses were likely to be used in clinical practice (see section 4.9). The Committee also considered

whether appraising ustekinumab 45 mg alone could 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.

4.17   The Committee considered the analyses incorporating the patient access scheme provided by the company and the ERG for the rapid review of NICE technology appraisal guidance 313. It noted that the ERG had corrected errors in the company's model, and considered these corrections appropriate. The Committee considered that it would have been preferable to include the additional costs associated with the patient access scheme in the model, although it understood that the effects of these costs on the results would be small. The Committee noted that the company had incorporated the effect of conventional management on skin symptoms in its base case, and that the ERG had incorporated this assumption along with the assessment of treatment response at week 24 for both conventional management and ustekinumab and a 40-year time horizon in its scenario analysis. The Committee considered that the probabilistic ICERs, when available, were more informative than the deterministic ICERs. It concluded that the ERG's scenario analysis (see section 3.40) reflected the Committee's preferred assumptions and therefore provided the most informative results and the most plausible ICERs, although it noted that the ICERs would decrease if the response to conventional management were assessed at week 12.

4.18   The Committee considered the cost effectiveness of ustekinumab in the TNF-alpha inhibitor-naive population. It 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 4.2). The Committee noted that, with the patient access scheme, ustekinumab was the lowest-cost biological treatment but was extendedly dominated (that is, was more expensive and less effective than a combination of 2 comparators). Moreover, the Committee noted that the cost-effectiveness analyses were subject to uncertainty because of the potential effect of a possible increase in HAQ-DI during ustekinumab treatment, which would be expected to reduce the cost effectiveness of ustekinumab. The Committee concluded that ustekinumab is not a cost-effective option, compared with TNF-alpha inhibitors, for treating psoriatic

arthritis in people who have not previously had TNF-alpha inhibitors.

4.19   The Committee also considered the cost effectiveness of ustekinumab in people who have not previously had TNF-alpha inhibitors and for whom TNF-alpha inhibitors are contraindicated. It considered that this population comprises people for whom a TNF-alpha inhibitor would otherwise be considered (as per the criteria described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis, see section 4.1). In this population, the Committee considered that conventional management is the most appropriate comparator. It emphasised that ustekinumab is innovative for this population, because it potentially fulfils an important unmet need. It noted that 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 which 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 noted that when the patient access scheme was applied and its preferred assumptions were incorporated, the most plausible ICER was £21,900 per quality-adjusted life year (QALY) gained, compared with conventional management. Although it considered that this ICER was still subject to uncertainty because of the possible increase in HAQ-DI during ustekinumab treatment (see section 4.11), the Committee noted that the ICER would be lower if the response to conventional management were assessed at week 12. It was also conscious that there is considerable unmet need in this population and that ustekinumab is an innovative treatment in this setting. The Committee therefore concluded that ustekinumab is a cost-effective option for treating psoriatic arthritis in people who have not previously had TNF-alpha inhibitors and for whom TNF-alpha inhibitors are contraindicated.

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 company's original submission. The Committee therefore considered the exploratory sequencing analysis initially presented by the ERG, noting that the analysis was reproduced by the company in its rapid review

model. This analysis assessed the cost effectiveness of ustekinumab and TNF-alpha 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, and comprised an incremental comparison of ustekinumab, TNF-alpha inhibitors and conventional management. The ERG and the Committee acknowledged that this analysis is subject to considerable uncertainty. This was 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 experts 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. With the patient access scheme and the preferred assumptions incorporated, the Committee noted that in the incremental analysis, the most plausible ICER for ustekinumab was £25,400 per QALY gained (compared with conventional management). The Committee was aware that the ICER was subject to uncertainty because of the possible increase in HAQ-DI during ustekinumab treatment, and noted that the ICER would decrease if the response to conventional management were assessed at week 12. The Committee understood that this analysis was uncertain, but concluded that it was reasonable to recommend ustekinumab as a treatment option for people who have previously had 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. With the patient access scheme and preferred assumptions incorporated, the Committee considered that the most plausible ICER compared with conventional management in the TNF-alpha

inhibitor-exposed population was £25,300 per QALY gained. Similarly to the TNF-alpha inhibitor-naive population, the Committee understood that this ICER was still subject to uncertainty because of the possible increase in HAQ-DI during ustekinumab treatment, although it noted that the ICER would decrease if the response to conventional management were assessed at week 12. The Committee was also aware of the considerable unmet need in this population. The Committee concluded that ustekinumab is a cost-effective option for treating psoriatic arthritis in people who have previously had TNF-alpha inhibitor therapy and for whom TNF-alpha inhibitors as a class have failed.

4.22   The Committee discussed the recommendation to stop treatment based on an inadequate PsARC response in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis. The Committee noted that the economic analyses (in all populations) were based on the assumption that people whose psoriatic arthritis has not shown an adequate PsARC response at 24 weeks stop treatment with ustekinumab. The Committee considered that the recommendation to stop treatment based on an inadequate PsARC response (as defined in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis) was also appropriate for ustekinumab (assessed at 24 weeks). It noted that some people may have physical, sensory or learning disabilities or communication difficulties that could affect their responses to components of the PsARC, and concluded that this should be taken into account when using the PsARC.

4.23   The Committee considered evidence from the company on the innovative nature of ustekinumab. It heard from the clinical experts 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. The Committee noted that there is 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 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.

4.24   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 the clinical experts 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.

5 Implementation

5.1 [Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has psoriatic arthritis and the healthcare professional responsible for their care thinks that ustekinumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

7 Appraisal Committee members, guideline representatives 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 Aomesh Bhatt

Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

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

Dr Ian Campbell

Honorary Consultant Physician, Llandough Hospital, Cardiff

Tracey Cole

Lay Member

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

Christopher Earl

Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Gillian Ells

Prescribing Adviser – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh

Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

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

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 Metropolitan Borough Council

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

Dr Mohit Sharma
Consultant in Public Health, Public Health England

Dr Peter Sims
GP, Devon

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

Cliff Snelling
Lay Member

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

8 Sources of evidence considered by the Committee

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

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). Companies were also invited to make written submissions. Professional or expert and patient or carer groups, and other consultees, had the opportunity to make written submissions. Companies, professional or expert and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company:

- Janssen

Professional or expert and patient or 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

Other consultees:

- Department of Health

- NHS England

- Welsh Government

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

- 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

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on ustekinumab by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Dr Eleanor Korendowych, Consultant Rheumatologist, nominated by British Society for Rheumatology – clinical expert

- Professor Dennis McGonagle, Professor of Investigative Rheumatology, nominated by Janssen – clinical expert

- David Chandler, Chief Executive of the Psoriasis and Psoriatic Arthritis Alliance, nominated by Psoriasis and Psoriatic Arthritis Alliance – patient expert

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

- Janssen

Update information

March 2017: Under the original patient access scheme the company provided 2x45-mg pre-filled syringes, for patients who needed the higher dose of 90-mg, at the same total cost to the NHS as for a single 45-mg pre-filled syringe. The patient access scheme has been withdrawn because the company now provides a 90-mg vial at the same cost as the 45-mg vial.

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