The Clinical and Cost-effectiveness of Ustekinumab for the treatment of Psoriatic Arthritis: A Critique of the Evidence

In no particular order: Joanne O’Connor1\*, Stephen Rice1, Alison Smith1, Mark Rodgers1, Rocio Rodriguez Lopez1 Dawn Craig1, Nerys Woolacott1.

1Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD, UK.

\*Corresponding author:

e-mail: joanne.oconnor@newcastle.ac.uk

Article Type: Review Article

**Acknowledgments** This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project number 10/51/01) and has been published as part of a compendium of ERG articles in *Health Technology Assessment*. See the HTA programme website for further project information (http://[www.hta.ac.uk](file:///C:\Users\njo18\AppData\Local\Microsoft\Windows\Documents%20and%20Settings\CP2\Local%20Settings\Temporary%20Internet%20Files\Content.IE5\47G36ZQ3\www.hta.ac.uk)). This summary of the ERG report was compiled after the Appraisal Committee’s review. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of NICE or the Department of Health.

The ERG would like to thank Ian Bruce for providing clinical advice throughout the project.

This summary has not been externally peer reviewed by *PharmacoEconomics*.

**Conflicts of Interest** Joanne O’Connor, Stephen Rice, Alison Smith, Mark Rodgers, Rocio Rodriguez Lopez, Dawn Craig and Nerys Woolacott have no competing interests.

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**Contributors:** JO, AS, DC, MR, NW and RL all formed part of the Evidence Review Group that produced the Evidence Review Group Report that this paper describes. Ian Bruce provided clinical advice to the ERG. SR contributed to later ERG submissions that are included in this paper. JO, AS and SR wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript. JO is the guarantor for the overall content.

## Abstract

The National Institute for Health and Clinical Excellence (NICE) invited the manufacturer of ustekinumab (Janssen) to submit evidence for the clinical and cost effectiveness of ustekinumab for the treatment of active psoriatic arthritis (PsA) as part of the Institute’s single technology appraisal (STA) process. The Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE) Technology Appraisal Group at the University of York was commissioned to act as the independent evidence review group (ERG). This article provides a description of the ERG review of the manufacturer’s evidence submission, and summarizes the NICE Appraisal Committee’s (AC) final guidance (TA340) issued in June 2015.

The manufacturer presented evidence on ustekinumab for two patient populations: (i) a tumour necrosis factor-α (TNFα) - inhibitor naïve population, who had not previously received any TNFα inhibitors (biologics); and a TNFα inhibitor-exposed population, who had previously received at least one TNFα inhibitor. The clinical evidence for ustekinumab was derived from two randomised controlled trials (PSUMMIT 1 and 2), in which a total of 927 patients who not responded to previous disease-modifying antirheumatic drug therapies received 45mg ustekinumab, 90mg ustekinumab, or placebo. These data suggested that ustekinumab is more effective than placebo over 16-24 weeks in terms of both joint and skin response. In the absence of head-to-head comparisons between different biologics (ustekinumab, golimumab, etanercept, adalimumab and infliximab), the manufacturer conducted a network meta-analysis (NMA) to estimate the relative efficacy of treatments for the TNFα-inhibitor-naïve population. Results of this analysis were marked as academic in confidence and are therefore not reported. For the TNFα inhibitor exposed population, the clinical analysis was limited to ustekinumab versus conventional management only, and was based on a subgroup of 180 patients from the PSUMMIT 2 trial. The ERG raised concerns relating to the lack of data on long term efficacy of ustekinumab, the limited data available for the exposed population, and the lack of consideration of the sequential use of treatments.

Based on the manufacturer’s original model, the ERG found ustekinumab to be dominated by golimumab in the anti-TNF inhibitor naïve population, and had an ICER of £29, 843/QALY versus conventional management in the exposed population. The ERG’s analyses highlighted the fact that there is significant uncertainty around the model results. In addition the ERG’s exploratory cost-effectiveness analysis, which incorporated the sequential use of TNFα inhibitors, suggested that ustekinumab would not be cost-effective if it were used as second-line treatment.

The initial NICE recommendations asserted that ustekinumab was not recommended for treating active PsA. However, the manufacturer submitted a post-consultation model which included a patient access scheme (PAS), halving the unit cost of ustekinumab 90 mg to £2,147 (the same as a 45mg dose). The NICE final recommendations were that, dependant on the inclusion of the PAS, ustekinumab is recommended as an option, along or in combination with methotrexate, for treating active PsA in adults only when treatment with TNFα inhibitors is contraindicated but would otherwise be considered, or the person has previously had treatment with one or more TNFα inhibitors, which has failed.

# Key points for decision makers

* Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treatment active psoriatic arthritis in adults in the following scenarios:
  + When treatment with tumour necrosis factor-α (TNFα) inhibitors is contraindicated but would otherwise be considered, or
  + The person has already had with one or more TNFα inhibitors.
* Ustekinumab is only recommended if the company provides the 90mg dose of ustekinumab for people who weight more than 100kg at the same cost as the 45mg dose, as agreed in the patient access scheme.

## Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing guidance to the National Health Service (NHS) in England and Wales on the use of new and existing health technologies. NICE’s single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor [1]. Typically it is used for new pharmaceutical products close to launch. The evidence for an STA is provided by the manufacturer to NICE and reviewed by an independent evidence review group (ERG) which is supported by a clinical advisor. The ERG produces a report which provides a critical appraisal of the clinical and cost-effectiveness analysis as well as some additional analyses [2]. Consultees, clinical experts and patient representatives also provide further information to the NICE appraisal committee.

The NICE appraisal committee considers all the evidence submitted, including the ERG’s independent assessment and testimonies from other experts or stakeholders, to deliberate on whether the technology should be recommended as a clinical and cost-effective use of NHS resources [1]. If the recommendations from the appraisal committee are restrictive, an appraisal consultation document (ACD) is produced, which is distributed to consultees and commentators for comment and is made available on the NICE website for wider comment [1]. A second NICE committee meeting is conducted to consider comments on the ACD (if produced), and to make final recommendations for the technology, which are outlined in the final appraisal determination (FAD) document [1]. It is possible for organisations representing patients and carers, healthcare professionals and manufacturers to appeal the final recommendations made for the technology [1].If no appeals are made against the recommendations in the FAD, or an appeal is not upheld, the final recommendations are issued as NICE guidance [1]. NHS providers are legally obliged to fund technologies that are recommended in NICE technology guidance, within their licenced indication [1]. This article presents a summary of the ERG’s independent critique of the manufacturer’s submission to NICE and its role in the subsequent development of the NICE guidance on ustekinumab for the treatment of patients with psoriatic arthritis.

Full details of the NICE appraisal and the relevant documents can be found on the NICE website [3].

## Decision Problem

Psoriatic arthritis (PsA) is a chronic inflammatory disease closely associated with psoriasis, which affects the skin, joints and soft tissue [4]. PsA is closely associated with psoriasis; 5-7% of people with psoriasis and 40% with extensive skin disease have psoriatic arthritis [5-9].

Current treatment for PsA typically begins with disease-modifying anti-rheumatic drugs (DMARDs) or non-steroidal anti-inflammatory drugs (NSAIDS), which aim to relieve symptoms, slow disease progression and prevent disability. For patients with active and progressive PsA who have re­sponded inadequately to at least two DMARDs, NICE guidance recom­mends four alternative licensed tumour necrosis factor-α inhibitors (TNF-α inhibitors): etan­ercept, infliximab, adalimumab and golimumab [10,11]. NICE guidance states that treatment should normally be started with the least expensive TNF-α inhibitors drug (taking into account drug administration costs, required dose and product price per dose) [2]. Although not universal, sequential use of TNF-α inhibitors is established practice in the NHS: upon failure of TNF-α inhibitors patients may switch to a different TNF-α inhibitor. Failing that despite the previous lack of efficacy of DMARDs and NSAIDs, patients withdraw back to these sub-optimal conventional management strategies (CMS) as there is no current alternative for these patients.

## Ustekinumab is a monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin (IL-12) and interleukin-23 (IL-23) [2]. Ustekinumab, alone or in combination with methotrexate, has a European marketing authorisation for the treatment of active PsA in adult patients when response to previous DMARDs has been inadequate [3]. In addition ustekinumab has a marketing authorisation for the treatment of moderate to severe plaque psoriasis in adults and adolescent patients from the age of 12 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies and is currently recommended by NICE as a treatment for adults with moderate to severe plaque psoriasis [11]. It is expected that both indications for ustekinumab (plaque psoriasis and PsA) would cover approximately 27,000 patients in England and Wales; 7,000 of these being patients with PsA [3]. For PsA, the recommended dose of ustekinumab is 45mg, administered subcutaneously; an initial dose of 45mg is followed by a dose four weeks later and further doses every 12 weeks after that [2]. Alternatively, for patients weighing over 100kg a higher 90mg dose may be used [2].The Independent ERG Review

The company (Janssen) submitted evidence to NICE on the clinical and cost-effectiveness of ustekinumab for the treatment of active and progressive PsA in patients who have responded inadequately to previous DMARD therapies. The Centre for Reviews and Dissemination and the Centre for Health Economics at the University of York were commissioned to act as the Evidence Review Group (ERG) to critically appraise the manufacturer’s submission. The ERG report comprised a critical review of the clinical and cost effectiveness of ustekinumab based on the manufacturer’s submission. The aims of the review were to assess whether the manufacturer’s submission conformed to the methodological guidelines issued by NICE, and to assess whether the company’s interpretation and analysis of the evidence were appropriate. Additionally, the ERG identified areas in the company’s submission requiring clarification, for which the manufacturer provided additional evidence [2].

### Patient Population

The manufacturer presented two scenarios for the use of ustekinumab for PsA, using patient populations at different stages of the treatment pathway:

1. Patients who had responded inadequately to DMARDs but not yet progressed to TNF-α inhibitors (TNF-α inhibitor naïve patients); and
2. Patients who had previously received one or more TNF-α inhibitors which had failed (due to one of several reasons) and were moving on to treatment with an alternative TNF-α inhibitor (TNF-α inhibitor exposed patients).

For each of these populations the manufacturer considered different comparators:

* For TNF-α inhibitor naïve patients, ustekinumab was compared with all licensed TNF-α inhibitors;
* For the TNF-α inhibitor exposed patients, ustekinumab was compared with conventional management only.

### 3.1.1 Critique of Patient Population

The ERG noted that neither of the manufacturer’s scenarios fully reflected UK clinical practice, where up to four TNF-α inhibitors can be administered in (no fixed) sequence. The TNF-α inhibitor naïve scenario considers the specific case of ustekinumab as an alternative to first-line TNF-α inhibitor treatment. In the TNF-α inhibitor exposed scenario, use of conventional management as the sole comparator implies that patients have exhausted all TNF-α inhibitor options; this scenario therefore represents the specific case of ustekinumab as an end-line treatment option, after a sequence of up to four TNF-α inhibitors has been tried and failed. As such the manufacturer did not evaluate the effectiveness of ustekinumab as an alternative to a second- or third-line TNF-α inhibitor, which is also a relevant comparison for patients being treated with sequential TNF-α inhibitors. The manufacturer’s analysis therefore only addresses a restricted part of the decision problem, placing ustekinumab either at the beginning or the end of the TNF-α inhibitor treatment sequence.

## Clinical Evidence

The manufacturer conducted a systematic review to identify relevant evidence on the clinical effectiveness of ustekinumab for the treatment of active and progressive PsA [2]. The majority of evidence on the efficacy of ustekinumab was derived from two randomised controlled trials (PSUMMIT 1 and PSUMMIT 2), identified in this review [12-13].

Across both trials a total of 927 patients who had not responded to previous DMARD therapies were randomly assigned to receive 45mg ustekinumab, 90mg ustekinumab, or placebo, which is assumed to equate to CMS. The PSUMMIT 2 trial included a subgroup of 180 patients who had previously received at least one TNF-α inhibitor [12]. In both trials at week 16 patients who had not respond to active treatment entered a blinded “early-escape”, in which non-responders in the conventional management arm received 45mg ustekinumab, and non-responders in the ustekinumab 45mg arm received the higher 90mg dose [12-13]. At week 24 all remaining patients in the placebo group received ustekinumab 45mg [12-13].

The primary outcome of both trials was treatment response defined as a 20% or greater improvement in joint condition according to the American College of Rheumatology assessment criteria (ACR20) at 24 weeks [12-13]. Secondary outcomes included response rates for ACR50/70, Psoriasis Area and Severity Index (PASI) 75/90, the Disability Index of the Health Assessment Questionnaire (HAQ-DI) and radiographic progression assessed by changes in modified van der Heijde-Sharp Score (vdH-S) and PsA Response Criteria (PsARC) [12-13].

Data from the PSUMMIT trials suggest that for TNF-α inhibitor naïve and for TNF-α exposed patients, ustekinumab is more effective than placebo over 16-24 weeks in terms of both joint (ACR 20/50/70, PsARC) and skin (PASI 75) response (see **Table 1**)[12-13]. In response to the ERG’s query, the manufacturer provided additional data on outcomes up to 52 weeks, which showed that the benefits seen at 16-24 weeks are likely to persist for at least 52 weeks for the TNF- inhibitor naïve population.

Evidence from the PSUMMIT 2 trial subgroup showed that overall response rates were lower for the TNF-α inhibitor exposed population compared to the naïve population but there was no statistically significant difference in the efficacy of ustekinumab between TNF-α inhibitor naïve and experienced patients [12]. There was no obvious difference between ustekinumab doses or interactions between dose and prior TNF-α inhibitor exposure. Treatment effects were not significantly different for 45mg and 90mg doses of ustekinumab (Table 1)

**Table 1. Ustekinumab efficacy data from PSUMMIT 1 and PSUMMIT 2 trials**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome | Ustekinumab 45mg | Ustekinumab 90mg | Placebo | Ustekinumab 45mg [RR] | Ustekinumab 90mg [RR] |
| PSUMMIT 1 (TNF-α inhibitor naïve, n=615) | | | | | |
| ACR 20 | 42.4% | 49.5% | 22.8% | 1.86 | 2.17 |
| ACR 50 | 24.9% | 27.9% | 8.7% | 2.85 | 3.20 |
| ACR 70 | 12.2% | 14.2% | 2.4% | 5.02 | 5.86 |
| PsARC | 56.1% | 64.7% | 37.4% | 1.50 | 1.73 |
| PASI 75 | 57.2% | 62.4% | 11.0% | 5.22 | 5.70 |
| PSUMMIT 2 (TNF-α inhibitor naïve, n=132) | | | | | |
| ACR 20 | 53.5% | 55.3% | 28.6% | 1.87 | 1.94 |
| ACR 50 | 20.9% | 31.9% | 7.1% | 2.93 | 4.47 |
| ACR 70 | 9.3% | 12.8% | 4.8% | 1.95 | 2.68 |
| PsARC | 55.8% | 57.4% | 38.1% | 1.47 | 1.51 |
| PASI 75 | 58.3% | 62.5% | 10.0% | 5.83 | 6.25 |
| PSUMMIT 2 (TNF-α inhibitor exposed, n=180) | | | | | |
| ACR 20 | 36.7% | 34.5% | 14.5% | 2.53 | 2.38 |
| ACR 50 | 15.0% | 15.5% | 6.5% | 2.33 | 2.41 |
| ACR 70 | 5.0% | 5.2% | 1.6% | 3.10 | 3.21 |
| PsARC | 55.0% | 46.6% | 25.8% | 2.13 | 1.80 |
| PASI 75 | 45.5% | 48.8% | 2.0% | 22.7 | 24.39 |
| All data are presented as proportion of participants meeting criteria unless otherwise indicated  ACR= American College of Rheumatology; PASI=Psoriasis Area and Severity Index; PsARC=Psoriatic Arthritis Response Criteria; RR=relative risk.  Placebo is assumed to equate to conventional management strategies (CMS)  95% Confidence Intervals for RR results were marked as confidential in the manufacturer’s response to clarifications and therefore could not be reported. | | | | | |

In the absence of head-to-head comparisons of the relative efficacy between different biologics (ustekinumab, golimumab, etanercept, adalimumab and infliximab), the manufacturer conducted a network meta-analysis (NMA) incorporating nine placebo controlled RCTs to estimate the relative efficacy of the five relevant biologics and conventional management in the TNF-α inhibitor naïve population. Separate networks were constructed for three outcomes (PASI75, PASI90 and PsARC) and across two time points (12 -16 weeks and 24 weeks). As outcomes at 24 weeks only were available for ustekinumab, these were assumed equal to the outcomes at 12-16 weeks for the NMA. The results of the NMA were marked as academic in confidence and so the results cannot be reported here.

With the exception of a slightly higher proportion of injection site reactions for ustekinumab 90mg observed in the PSUMMIT trials (1% 90mg vs. 0.6% 45mg vs. 0.4% placebo), the included trial data did not suggest any obvious excess in adverse events for ustekinumab treated patients [12-13].

### Critique of the Clinical Evidence

The PSUMMIT trials from which evidence on the efficacy of ustekinumab was derived were of adequate methodological quality. The results obtained from these trials are likely to be valid, and indicate that ustekinumab is a more effective treatment than placebo over 16 to 24 weeks, and that these benefits are likely to persist for at least 52 weeks. However, the interruption of the placebo-controlled phase at week 16 and the termination of the controlled phase altogether at 24 weeks mean that the trials only provide a brief comparison for a chronic condition such as PsA. No data was available on longer term radiographic progression.

For the TNF-α inhibitor exposed population, the analysis was based on a subgroup of 180 patients from the PSUMMIT 2 trial who had received a varied number of prior TNF-α inhibitors [12]. Thus data for participants who could be considered truly ‘TNF-α inhibitor refractory’ (i.e. having exhausted all biological treatments sequentially and for whom conventional management would be the appropriate comparator) is sparse (numbers confidential and so cannot be reported). Also, it was unclear which biologic treatments these patients had received and the relative efficacy of the treatments when given in the different positions within the sequence.

Several of the trials included in the NMA (including the PSUMMIT trials) included participants who had never received prior DMARD therapy and where reported the mean number of prior DMARDs was typically fewer than two; this suggests that the NMA population may be less severe than that routinely considered for biologic treatment in practice (where patients are required to have failed two or more prior DMARDs). Nevertheless the trials were broadly similar in terms of disease severity and functional status, so the NMA results should be valid for the population assessed.

PsARC and PASI response rates used for ustekinumab in the manufacturer’s NMA were derived from a subset of patients from the PSUMMIT trials who were treated according to a strict weight-based dosing regimen. That is, data was only used on participants in the 45mg arm who weighed less than 100kg, and participants in the 90mg arm who weighed more than 100kg. This resulted in a significant amount of data being discarded, and the ERG believed that this strict weight-based dosing does not fully reflect the license for ustekinumab, since all patients may commence treatment on the 45mg dose, regardless of weight. The ERG conducted a sensitivity analysis for the TNF-α inhibitor naïve population, using the full intention-to-treat (ITT) population. In general the results were fairly similar across both the weight-based and full ITT populations.

## Cost-effectiveness Evidence

The manufacturer constructed a combined decision tree and Markov model to compare adalimumab, etanercept, infliximab, golimumab and ustekinumab versus conventional management for TNF-α inhibitor naïve patients and to compare ustekinumab with conventional management only for TNF-α inhibitor exposed patients. A time horizon of 52 years was used. The decision tree structure is presented in Figure 1 [2]. The Markov model structure is presented in Figure 2[2].

The key inputs in the model were PsARC response rates, HAQ change for responders and non-responders and PASI score changes. This information is not presented here as a significant portion is academic in confidence and therefore redacted.

Figure 1: Decision tree structure

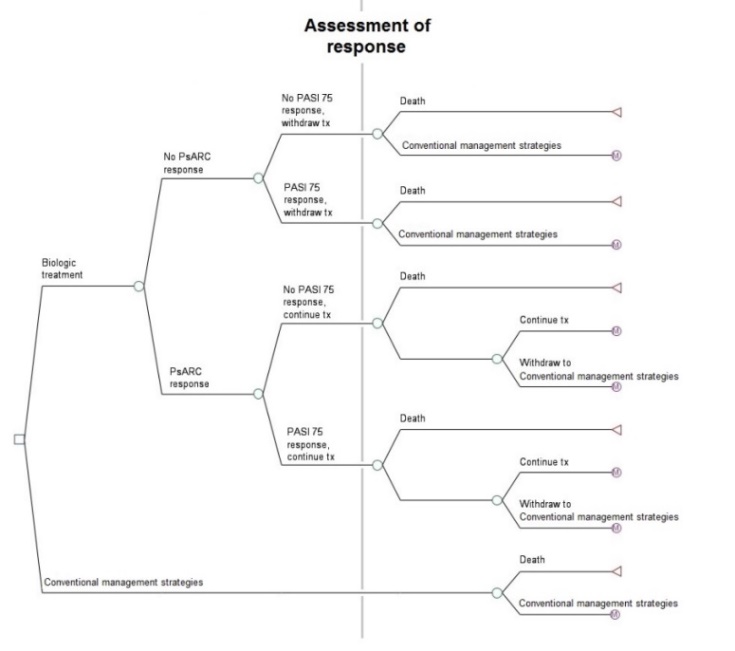
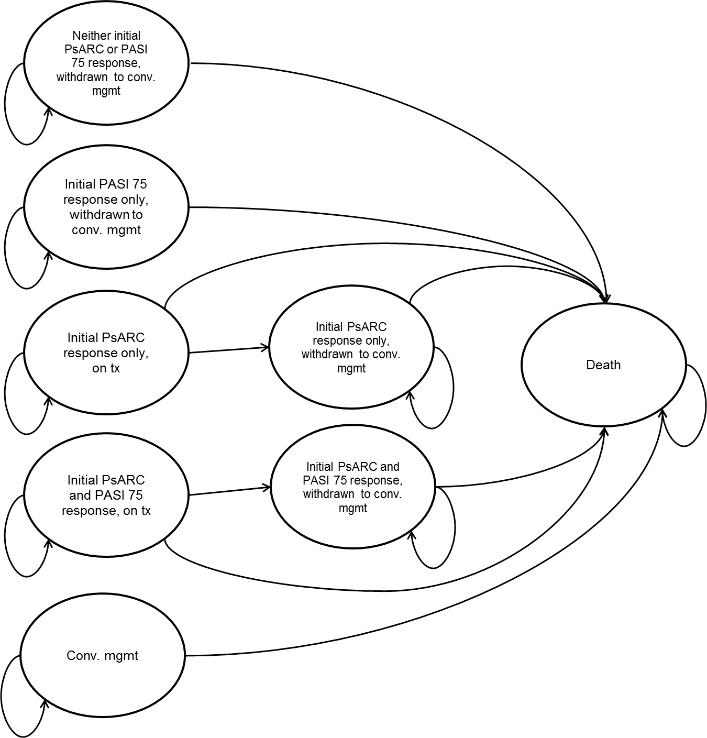


Figure 1: Markov model structure



Patients achieving an initial PsARC response at 12 weeks for TNF-α inhibitors, and 24 weeks for ustekinumab, were considered to be responders and continued active treatment. Non-responders were withdrawn to conventional management. Patients remaining on active treatment were subject to a constant withdrawal rate to account for long-term treatment discontinuation. Treatment effectiveness was modelled as an improvement in PASI and Health Assessment Questionnaire (HAQ) scores from baseline, which were both secondary outcomes in the PSUMMIT trials. Upon withdrawal to conventional management HAQ and PASI scores rebounded to baseline levels, with HAQ scores assumed to gradually deteriorate over time, according to the “natural history” of HAQ.

For the TNF-α inhibitor naïve population, PASI response rates were obtained from the manufacturer’s NMA, and HAQ score changes were derived from a previously conducted NMA [14]. For the TNF-α inhibitor exposed population, effectiveness estimates were derived from the PSUMMIT 2 exposed subgroup [12]. If a patient achieved a PASI response great enough to continue treatment, a fixed improvement in PASI score based on PASI response was assumed. Conventional management was assumed to have no impact on skin symptoms. It was also assumed that, for people who withdraw from biological therapy, the PASI score would rebound to a score based on the effect of conventional management (rather than the baseline score).

Patient quality-adjusted life-years (QALYs) and health state costs were estimated as a function of HAQ and PASI scores. HAQ- and PASI-related costs were based on estimates used in the previous manufacturer’s submission for golimumab [14]. Medical resource use requirements for patients on ustekinumab were assumed to be the same as for patients on other biologics. Resource use costs were taken from NHS Reference Costs [15]. TNF-α inhibitor acquisition costs were derived from the British National Formulary [16]. Each 45mg unit of ustekinumab costs £2,147. Drug administration costs were only applied to infliximab, which requires intravenous infusion at hospital. Detailed deterministic and probabilistic sensitivity analyses were undertaken.

Minor errors in the manufacturer’s original model and its inputs were corrected by the ERG and agreed by the manufacturer, which included re-calculating the baseline HAQ and PASI values.

For the TNF-α inhibitor naïve population, the ERG corrected model found that ustekinumab was dominated by golimumab (with golimumab being less costly and more effective than ustekinumab [3]. The incremental cost-effectiveness ratio (ICER) for ustekinumab versus conventional management was £23,508 per QALY gained (Table 2).

**Table 2. Probabilistic results for ERG’s corrected version of the manufacturer’s base-case model (TNF-α inhibitor naive population)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total Costs (£)** | **Total QALYs** | **Incremental Costs (£)** | **Incremental**  **QALYs** | **ICER vs. CMS (£/QALYs)** | **ICER vs. next best alternative (£/QALYs)** |
| Conventional Management | 33,113 | 4.60 |  |  |  |  |
| Golimumab | 62,794 | 6.83 | 29,681 | 2.23 | 13,335 | 13,335 |
| Adalimumab | 64,493 | 6.37 | 1,699 | -0.45 | 17,716 | Dominated |
| Ustekinumab | 70,343 | 6.18 | 7,548 | -0.64 | 23,508 | Dominated |
| Etanercept | 72,288 | 6.91 | 9,493 | 0.09 | 16,942 | 109,900 |
| Infliximab | 134,900 | 7.11 | 62,613 | 0.20 | 40,597 | 321,032 |
| QALY= Quality-adjusted Life Year; CMS= Conventional Management Strategies. | | | | | | |

For the TNF-α inhibitor exposed population, the ERG corrected model found that the ICER for ustekinumab versus conventional management was £29,843 per QALY gained (see Table 3). These results were very similar to the manufacturer’s original base case results.

Table 2: Probabilistic results for ERG’s corrected version of the manufacturer’s base-case model (TNF-α inhibitor exposed population)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total Costs (£)** | **Total QALYs** | **Incremental Costs (£)** | **Incremental**  **QALYs** | **ICER vs. CMS (£/QALYs)** |
| Conventional Management | £36,008 | 2.79 |  |  |  |
| Ustekinumab | £77,208 | 4.17 | £41,200 | 1.38 | £29,843 |
| **QALY= Quality-adjusted Life Year; CMS= Conventional Management Strategies.** | | | | | |

Results of sensitivity analysis, for both the TNF-α inhibitor naïve and TNF-α inhibitor exposed population, showed that the results were particularly sensitive to the HAQ natural history rate of deterioration, the time horizon used and whether the treatment response was assessed at 12 or 24 weeks.

### Critique of the Cost-effectiveness Evidence

In general, the ERG considered the manufacturer’s economic evaluation to be of good quality, using an appropriate structure (although it did not facilitate testing structural assumptions) and meeting the requirements of the NICE reference case. However, the ERG had concerns about several assumptions used in the model, discussed below.

*HAQ Rebound*

A key assumption in the model is that upon treatment discontinuation patients’ HAQ score rebounds to the baseline level, and subsequently deteriorates in line with the natural progression of HAQ. The manufacturer’s model allowed for a sensitivity analysis in which HAQ was assumed to rebound to the point where patients would have been had they remained on conventional management i.e. the point on the natural progression line for patients who received no biologic treatment. This is considered by the ERG to be an important scenario, as it represents a “worst case scenario” for HAQ rebounding. Although the model allowed for this analysis, the results for this scenario were not reported in the manufacturer’s submission. This analysis was therefore re-run by the ERG. Ustekinumab remained dominated by golimumab, but the ICER versus conventional management increased from £23,508/QALY (base case) to £41,500/QALY. Similarly for the TNF-α exposed population, assuming HAQ rebounds to the natural progression point resulted in the ICER for ustekinumab versus conventional management increasing from £29,843/QALY to £52,408/QALY.

There is also uncertainty as to the point and speed at which HAQ levels may be expected to rebound to the baseline level. The manufacturer assumed that HAQ would immediately rebound to the baseline score upon treatment discontinuation. It may be that HAQ scores would gradually worsen over a period of time prior to treatment withdrawal, especially in cases of withdrawal due to waning efficacy. The model did not easily facilitate further exploration of the issue, however it is expected that this scenario would again increase the ICERs, making all of the biologic treatments less cost-effective options.

*TNF-α inhibitor exposed population: ERG exploratory analysis*

The manufacturer suggested that ustekinumab provides a novel treatment option when TNF-α inhibitor treatment has failed using conventional management as the comparator [2]. However, although the manufacturer’s model implicitly assumed that the TNF-α inhibitor exposed patients had exhausted all TNF-α inhibitor treatment options and have no choice but to revert to non-biologic treatments, their model used evidence derived from a trial population who had experienced TNF-α inhibitors but who had not necessarily failed them as a class. It was clear from the PSUMMIT 2 patient characteristics that the sub-group of exposed patients were not all patients who have exhausted TNF-α inhibitor treatments [12]. Using conventional management as the only comparator is therefore only appropriate for a subgroup of this sub-population. The ERG performed an exploratory analysis where golimumab, adalimumab or etanercept were used as first line treatments and ustekinumab was compared with the other TNF-α inhibitors as second-line treatments. This analysis was based on some additional ERG exploratory analyses undertaken in a previous submission [10], which assumed patients were receiving second-line treatment due to failure of first line treatment as a result of either lack of efficacy or adverse events. Based on clinical literature on the relative risk of not responding to a second biologic drug compared to not responding to first-line drug, four sets of equations that adjusted the response rates and the withdrawal rates for TNF-α exposed patients were estimated 17, [18]. These adjusted rates were used to estimate costs and QALYs for ustekinumab when adalimumab, etanercept or infliximab were the failed first-line TNF-α inhibitors used.

Whilst observational evidence suggests diminishing response rates and treatment persistence associated with the sequential use of TNF-α inhibitors, there is no robust evidence for the relative efficacy of ustekinumab and TNF-α inhibitors when used as second or later-line therapy [10]. The NMA results suggest that most TNF-α inhibitors are more efficacious than ustekinumab in the TNF-α inhibitor naïve population, and no evidence is presented to suggest that the postulated reduction in efficacy of second, third, or fourth line TNF-α inhibitors would drop below the level of efficacy observed for ustekinumab in TNF-α inhibitors exposed patients.

This scenario is still not fully reflective of current practice in the UK (in that third line and fourth line treatment options were not included), however it does allow for the appropriate comparators for ustekinumab in a TNF-α inhibitor exposed (rather than exhausted) population to be considered. For all of these scenarios ustekinumab, as a second-line treatment, was either dominated by other treatments or was not cost-effective at a £30,000 per QALY threshold. It should be noted however that these results were subject to significant uncertainty due to limitations in the analysis and the strong assumptions made (which include the assumptions that second-line treatment would have the same probabilities of a PASI 75 response as in first-line treatment; that resource use estimates would be unchanged; and the more-up-to date clinical estimates provided in the manufacturer’s submission would not be used).

A short-coming of both the manufacturer’s submission and the ERG report is that neither analysis addressed where in the sequence of TNF-α inhibitors ustekinumab would fit, and neither explored all possible options. The manufacturer assumed that the effectiveness data collected in PSUMMIT 2 trial reflects end of line effectiveness and the ERG exploratory analysis assumed the effectiveness data reflects second-line effectiveness [12]. Neither assumption is robust; however the ERG exploratory analysis highlights the issues around the sequencing of TNF-α inhibitor treatments that should be taken into consideration in future research.

The following assumptions were subjected to further sensitivity analyses by the ERG, but were not found to have any meaningful impact on the results:

* Using data from the PSUMMIT trials based on intention-to-treat populations, instead of restricted weight- populations, in order to reflect how ustekinumab would be used in practice;
* Including data on HAQ change from baseline per PsARC responder/non-responder for ustekinumab from the weight-based PSUMMIT results instead of using the HAQ score changes from a previous NMA [17];
* Reducing the time horizon from 52 years to 40 years, to stay in line with previous submissions and enable comparisons [10, 11];
* Response to treatment in terms of PsARC response was assumed to occur at week 12, in line with previous submissions to enable comparisons [10, 11].

## Conclusions of the ERG Review

### TNF-α naïve population

Trials evidence demonstrates that ustekinumab is more effective than placebo over 16-24 weeks in terms of both joint (ACR 20/50/70, PsARC) and skin (PASI75/90) response, and these benefits are likely to persist for at least 52 weeks. However, when compared to TNF-α inhibitors for first-line biologic treatment, results of the manufacturer’s cost-effectiveness analysis indicate that ustekinumab is not a cost-effective alternative to current treatment options. Pairwise comparisons against conventional management found that golimumab, etanercept and adalimumab all had lower ICERs than ustekinumab. The ERG’s clarifications, corrections and additional analyses did not substantially change these results but did highlight the high levels of uncertainty in the analysis.

### TNF-α exposed population

Trials evidence suggests there is no convincing evidence of a substantial difference in the efficacy of ustekinumab between TNF-α inhibitor exposed patients and patients who have not received any prior TNF-α inhibitor treatment. Any benefit observed may be an artefact of the small number of patients in the analysis. (This evidence cannot be presented as the NMA was academic-in confidence.)

The ERG believed there were issues around the manufacturer’s analysis of the TNF-α inhibitor exposed population and the lack of consideration given to treatment sequencing and the use of ustekinumab as a second or third line treatment option, which may more appropriately reflect how ustekinumab would be expected to be used in UK clinical practice within the current sequencing approach to TNF inhibitors.

The ERG’s exploratory cost-effectiveness analysis, which incorporated the sequential use of TNF α inhibitor suggested that ustekinumab would be dominated or have an ICER above the NICE £30,000 upper threshold, regardless of the reason for the first-line treatment failure or which TNF-α inhibitor treatment was used as the first-time line treatment.

## Key Methodological Issues

### Clinical Effectiveness

The main areas of uncertainty in terms of clinical efficacy and drug safety were as follows:

* The lack of data on longer term efficacy and safety of ustekinumab
* The efficacy of ustekinumab in TNF-α inhibitor exposed patients compared to second- and third-line TNF-α inhibitors. A properly powered trial of ustekinumab versus TNF-α inhibitor therapy is required. Any such trial should clearly distinguish between prior TNF-α inhibitor exposure and TNF-α inhibitor class failure in its selection of participants so that reliable subgroup analyses could be undertaken.

### Cost Effectiveness

The main areas of uncertainty in terms of cost-effectiveness were as follows:

* The natural history of HAQ for patients on conventional management
* Rebound to HAQ on withdrawal from treatment. Further evidence is required to identify which scenario is most likely to reflect clinical reality
* The cost-effectiveness of ustekinumab in TNF-α inhibitor exposed patients compared to second- and third-line TNF-α inhibitors. Whilst the ERG exploratory analysis suggests that ustekinumab would not be cost-effective compared to alternative TNF-α inhibitors in this instance, this analysis was based on strong assumptions.

The decision question that has not been addressed by either the manufacturer or the ERG is where ustekinumab fits within sequential treatment TNF-α inhibitors and this is an area of further research that needs to be undertaken.

# Consideration of All Available Evidence

The NICE Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ustekinumab and considered the evidence presented in the manufacturer’s submission, ERG report and a range of additional sources including clinical experts, related health professionals, patient representatives and professional and specialist groups. It also took into account the effective use of NHS resources.

## Preliminary Guidance

The preliminary NICE recommendations, recorded in the appraisal consultation document (ACD), were that ustekinumab was not recommended for treating active PsA [2].

### 4.1.1. Manufacturer’s Response to the Appraisal Consultation Document (ACD) Consultation

The manufacturer submitted a response to the consultation document, which included some minor corrections to the original submission, in addition to the corrections made within the ERG report and the assumption that only 45mg dose was available. This response document did not change the conclusions made in the appraisal consultation document.

## Final Guidance

The final NICE recommendations, recorded in the final guidance to the NHS (TA313), were that ustekinumab was not recommended for treating active PsA [2]. However, the manufacturer subsequently submitted a revised analysis, which led to a revision of the NICE recommendations as outlined in TA340.

### 4.2.1 Manufacturer’s Post-Consultation Model

Following the publication of the FAD (TA313), the manufacturer submitted a revised economic analysis based on its post-consultation model. The manufacturer updated their model to incorporate some of the Committee’s requested amendments: the effect of conventional management on skin symptoms was modelled in the same way as the effects of biological drugs in the original model, where a fixed improvement in PASI score based on PASI response was assumed. It was also assumed that, for people who withdraw from biological therapy, the PASI score would rebound to a score based on the effect of conventional management (rather than the baseline score). This post-consultation model also included a patient access scheme (PAS). As reported in the FAD, the PAS consisted of a halving of the unit cost of ustekinumab 90 mg to £2,147; the same cost as a 45mg dose [2]. The ERG considered that the new assumption on the effect of conventional management on skin symptoms was appropriate.

A sequential treatment scenario analysis was also presented based on the ERG exploratory analysis which allowed ustekinumab to be compared with second-line TNF-α inhibitor treatment following failure of first-line TNF-α inhibitor treatment.

### 4.2.2 ERG Critique of the Manufacturer’s Post-Consultation Model

The ERG reviewed the manufacturer’s re-submitted post-consultation model, and conducted another analysis incorporating two more of the NICE committee’s preferred assumptions that could feasibly be implemented. These were using a 40 year time horizon and assessing response at 24 weeks for both ustekinumab and conventional management. During this rapid review of the post-consultation model, the ERG identified a number of errors in the manufacturer’s model and these were corrected. These ERG corrections, the inclusion of the NICE committee’s preferred assumptions as well as the inclusion of the PAS price for the 90mg dose of ustekinumab all had an effect on the final cost-effectiveness estimates. Whilst the inclusion of the NICE committee’s preferred assumptions increased the incremental cost-effectiveness ratios, both the ERG corrections and the inclusion of the PAS price for the 90mg dose of ustekinumab decreased the incremental cost-effectiveness ratios.

The results of the manufacturer’s post-consultation model and the ERG’s Alternative model (which incorporated the additional two NICE committee preferred assumptions) are presented in Table 4. Both of these results incorporated the PAS price for the 90mg dose and the ERG’s corrections of the identified errors. While the manufacturer presented results for TNF-α inhibitor naïve patients, TNF-α inhibitor exposed patients, and a sequential model, Table 4 presents the results for four populations highlighted in TA Guidance 313 [2].

Table 4: Summary of the results for the manufacturer’s post-consultation model and the ERG Alternative model using the PAS price

|  |  |  |
| --- | --- | --- |
| Population for ustekinumab | Manufacturer’s PAS model (*with* PAS) | ERG Alternative Model (*with* PAS) |
| TNF-α inhibitor naïve patients not contraindicated TNF-α inhibitors | Extendedly dominated | Extendedly dominated |
| TNF-α inhibitor naïve patients contraindicated to TNF-α inhibitors | £17,906 | £23,938 |
| TNF-α inhibitor exposed patients who withdrew from previous TNF-α inhibitor due to lack of efficacy or adverse reactions | £20,175 (sequential model) | £28,281 (sequential model) |
| TNF-α inhibitor exposed patients who have not responded to TNF-α inhibitors as a class | £20,068 (sequential model) | £27,307 (sequential model) |

The appropriate comparators for TNF-α inhibitor naïve patients who are able to have all TNF-α inhibitors, including ustekinumab (i.e. not contraindicated) were the other TNF-α inhibitors. When compared to the other inhibitors, ustekinumab was extendedly dominated in both the manufacturer’s and the ERG’s models.

The appropriate comparator for TNF-α inhibitor naïve patients who cannot have TNF-α inhibitors (i.e. contraindicated) was conventional management. In the manufacturer’s model, the ICER was estimated to be £17,906. When the ERG included the additional two Committee preferences, this increased the ICER to £23,938.

The appropriate comparator for TNF-α inhibitor exposed patients who did not respond to their first TNF-α inhibitor due to lack of efficacy or adverse reactions and were now receiving ustekinumab was the other TNF-α inhibitors as second-line treatments. This analysis used the sequential model in the ERG’s exploratory analysis. In the manufacturer’s model, the ICER was estimated to be £20,175. When the ERG included the additional two Committee preferences, this increased the ICER to £28,281.

The appropriate comparator for TNF-α inhibitor exposed patients who did not respond to all TNF-α inhibitors as a class and were now receiving ustekinumab was CMS. Again, this analysis used the sequential model in the ERG’s exploratory analysis. In the manufacturer’s model, the ICER was estimated to be £20,068. When the ERG included the additional two Committee preferences, this increased the ICER to £27,307.

# National Institute for Health and Care Excellence Final Guidance

On considering the responses to the preliminary guidance and the manufacturer’s PAS submission, the Committee updated the original FAD for ustekinumab [2]. The final FAD states that,

“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) α inhibitors is contraindicated but would otherwise be considered, or
* The person has had treatment with one or more TNF-α inhibitors.

Ustekinumab is recommended only if the company provides the 90mg dose of ustekinumab for people who weigh more than 100kg at the same cost as the 45mg dose, as agreed in the patient access scheme.”

# Interpretation of the Guidance

The sequential use of TNF-α inhibitors in the UK was a much discussed issue within this appraisal. Although not universally available, it was agreed within the Appraisal Committee meetings that sequential treatment with TNF-α inhibitors is administered in the UK. The appraisal for ustekinumab differs from previous appraisals of TNF-α inhibitors in that the use of the intervention as a second, third or fourth line treatment for psoriatic arthritis was explicitly considered. This presented a new challenge to the ERG to critique the appraisal, not just in terms of first-line treatment but also for subsequent sequential treatment with TNFα inhibitors. The literature around sequential use of TNFα inhibitors was limited and the challenge was to model the sequential use of TNFα inhibitors in a credible way.

The final recommendation for ustekinumab indicates that unless a patient is contraindicated to other treatment options, ustekinumab should be reserved for second-line treatment in patients with psoriatic arthritis.

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