# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using certolizumab pegol and secukinumab in the NHS in England. The appraisal committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using certolizumab pegol and secukinumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

**The key dates for this appraisal are:**

Closing date for comments: 27 January 2017

Third appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 7.

# 1 Recommendations

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

- it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or
- the person has had a TNF-alpha inhibitor but their disease has stopped responding after the first 12 weeks.

Certolizumab pegol is only recommended if the company provides it agreed in the patient access scheme.

1.2 Secukinumab alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:

- it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or
- the person has had a TNF-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks or
- TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).

Secukinumab is only recommended if the company provides it with the discount agreed in the patient access scheme.

1.3 Assess the response to certolizumab pegol and secukinumab after 12 weeks and 16 weeks of treatment respectively and only continue if there is clear evidence of response, defined as an improvement in at least

2 of the 4 Psoriatic Arthritis Response Criteria (PsARC) criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. 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 based on skin response (as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, recommendation 1.3).

1.4 When using the 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.

1.5 This guidance is not intended to affect the position of patients whose treatment with certolizumab pegol and secukinumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

# 2 The technologies

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| **Description of the technology** | Certolizumab pegol (Cimzia, UCB Pharma) is a biological therapy (a recombinant humanised antibody Fab' fragment against TNF-alpha and is conjugated to polyethylene glycol). |
| | Secukinumab (Cosentyx, Novartis) is a monoclonal antibody which targets interleukin 17A (IL-17A). |
| **Marketing authorisation** | Certolizumab pegol has a marketing authorisation in the UK for treating active psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug (DMARD) therapy has been inadequate, either:<br>• in combination with methotrexate or<br>• as monotherapy, if methotrexate cannot be tolerated or when continued treatment with methotrexate is inappropriate. |

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| | Secukinumab has a marketing authorisation in the UK for treating active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate, either:<br>• in combination with methotrexate or<br>• as monotherapy. |
| **Adverse reactions** | The most common treatment-related adverse events associated with certolizumab pegol and secukinumab include upper respiratory tract infections and nasopharyngitis. For full details of adverse reactions and contraindications, see the summary of product characteristics. |
| **Recommended dose and schedule** | Certolizumab pegol is given subcutaneously:<br>• as a loading dose of 400 mg at weeks 0, 2 and 4<br>• at a recommended maintenance dose of 200 mg every 2 weeks, after the loading dose. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. Methotrexate should be continued during treatment where appropriate.<br>Clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients whose disease has shown no evidence of therapeutic benefit within the first 12 weeks of treatment. |
| | Secukinumab is given subcutaneously:<br>• For patients with concomitant moderate to severe plaque psoriasis or patients whose disease has responded inadequately to TNF-alpha inhibitors, the initial recommended dose is 300 mg at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. Each 300 mg dose is given as 2 injections of 150 mg each.<br>• For other patients, the recommended initial dose is 150 mg at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4.<br>Consideration should be given to stopping treatment in patients whose disease has shown no response by 16 weeks of treatment. Some patients whose disease has shown an initial partial response may subsequently improve with continued treatment beyond 16 weeks. |

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| **Price** | Certolizumab pegol costs £357.50 per 200 mg prefilled pen or prefilled syringe. The company has agreed a patient access scheme with the Department of Health. The first 12 weeks of therapy with certolizumab pegol will be free of charge. |
| | Secukinumab costs £1,218.78 per 2 × 150 mg prefilled pen or syringe. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of secukinumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. |

# 3 Evidence

The appraisal committee (section 7) considered evidence from a number of sources. See the committee papers for full details of the evidence.

# 4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of certolizumab pegol and secukinumab, having considered evidence on the nature of psoriatic arthritis and the value placed on the benefits of certolizumab pegol and secukinumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

## *Clinical need and practice*

4.1 The committee heard from the patient experts about the nature of psoriatic arthritis and their experiences of treatment. It heard that psoriatic arthritis is a lifelong condition that has a serious effect on people's quality of life. It can develop at a young age, and affects all aspects of a person's life including education, career aspirations and family life. The committee heard from the patient experts that symptoms such as fatigue, pain and other associated comorbidities can have a major psychological impact.

The committee heard from the clinical experts that psoriatic arthritis not only affects joints and tendons but can also be associated with other debilitating conditions of the skin, bowel and eye and with metabolic syndrome. The committee recognised the importance to patients and clinical experts of addressing these associated comorbidities, which are not always captured in current research.

4.2 The committee heard from the clinical and patient experts that the psoriatic arthritis population is heterogeneous. Some people's disease responds to the first disease-modifying antirheumatic drug (DMARD), whereas other's disease may respond to a second or a third DMARD. Some people's disease may not respond at all. It heard from the clinical experts that in current UK clinical practice, people usually have 2 DMARDs before progressing to biological therapies (in line with guidelines from the British Society for Rheumatology and the European League Against Rheumatism, and in line with NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis). For people whose disease has poor prognostic markers, 2 or more DMARDs may be given at the same time to progress to biological therapies quicker. The committee was aware that the British Society for Rheumatology guidelines also mention that biological therapies (that is, tumour necrosis factor [TNF]-alpha inhibitors) can be considered in people with specific prognostic factors (including 5 or more swollen joints together with elevated C-reactive protein persisting for more than 3 months or structural joint damage caused by disease) when 1 DMARD has not worked. However, it was not convinced that this is established clinical practice in the NHS. Also, the committee heard from clinical experts that TNF-alpha inhibitors result in similar joint responses but different responses in comorbid illnesses, especially related to the skin. It also heard from clinical experts that people's disease may not respond to 1 TNF-alpha inhibitor but may respond to another and that although TNF-alpha inhibitors have similar safety profiles, people can have different adverse events. Therefore, to offer more options, there is a

clinical need for alternative therapies in the treatment pathway, particularly treatments with a different mechanism of action. The clinical experts commented that certolizumab pegol targets TNF-alpha and that secukinumab has a different mechanism of action, targeting interleukin 17A (IL-17A), which could potentially benefit people in whom TNF-alpha inhibitors are contraindicated or not tolerated. The committee heard from the clinical experts that both certolizumab pegol and secukinumab were effective therapies and that secukinumab 300 mg was particularly effective in severe psoriasis. The committee concluded that patients and clinicians consider certolizumab pegol and secukinumab to be important therapy options for people with active psoriatic arthritis whose disease has responded inadequately to previous DMARD therapies.

## *Clinical effectiveness*

4.3 Nineteen randomised controlled trials were identified by the assessment group as meeting the criteria for inclusion in the systematic review of short-term efficacy:

- 17 trials compared a biological therapy (and apremilast) with placebo, including RAPID-PsA (certolizumab pegol) and FUTURE 2 (secukinumab), which comprise the main clinical evidence.
- 2 were head-to-head comparisons comparing 1 biological therapy with another biological therapy.

4.4 The committee noted that many of the trials included in the systematic review were of good quality, and had a reasonably low risk of bias. The key outcomes of interest to the assessment group were the American College of Rheumatology response criteria, Psoriatic arthritis response criteria (PsARC), Psoriasis Area and Severity Index (PASI), health assessment questionnaire, and health assessment questionnaire conditional on PsARC data. The committee concluded that the trials were of good quality and the outcomes were appropriate.

### Companies' clinical effectiveness evidence

4.5 The committee mainly considered the clinical effectiveness evidence from the trials identified for certolizumab pegol (RAPID-PsA) and secukinumab (FUTURE 2). It noted that patients whose disease did not respond to a TNF-alpha inhibitor in the first 12 weeks of treatment (primary treatment failure) were excluded from RAPID-PsA.

4.6 The committee considered the clinical effectiveness evidence presented in the company submissions and discussed the results of the RAPID-PsA (certolizumab pegol) and FUTURE 2 (secukinumab) trials. It noted that both biological therapies showed short-term efficacy in treating psoriatic arthritis. When considering the full trial population, certolizumab pegol and secukinumab were associated with statistically significant improvements in all key outcomes. When the trial population was split into subpopulations based on previous biological therapy experience, the committee acknowledged that the results became difficult to compare. The committee noted that the comparison of RAPID-PsA and FUTURE 2 with clinical trials for other biological therapies (and apremilast) was not straightforward. Firstly, the committee noted that populations recruited in clinical trials have changed over time, with earlier trials excluding patients who had previously had biological therapies (that is, biological experienced) and later trials including such patients. There is variation across trials in the exclusion criteria for the biological-experienced subpopulation. The RAPID-PsA trial is more selective than the FUTURE 2 (secukinumab), PSUMMIT2 (ustekinumab) and PALACE (apremilast) trials in recruiting patients who have had treatment with a biological therapy because it excluded patients whose disease had not responded to a TNF-alpha inhibitor in the first 12 weeks of treatment (see section 4.5). Secondly, the committee noted that placebo response rates have increased markedly over time across the trials, referred to as 'placebo-creep'. The committee concluded that because these issues had either not been accounted for (secukinumab) or because it was unclear how they had been accounted for (certolizumab pegol) in the company

submissions, it was not possible to make reliable conclusions about the difference in the efficacy of certolizumab pegol and secukinumab using the companies' analyses.

4.7 The committee noted that treatment with certolizumab pegol and secukinumab resulted in statistically significant improvements in health-related quality-of-life measures and in improvements in extra-articular manifestations such as dactylitis (that is, inflammation of the fingers or toes) and enthesitis (that is, inflammation of tendons or ligaments). The committee noted that UCB submitted evidence on the impact of certolizumab pegol on pain and fatigue measured by the SF-36 and FASCA (Fatigue Assessment Scale) questionnaires. This was because the company believed that these outcomes may not have been captured in the assessment group's model, which is based on a mapping from the health assessment questionnaire and PASI to a utility score. The committee noted that the company provided values, but it was unable to determine the impact of any potential adjustment on the quality-adjusted life year (QALY) gained. The committee was satisfied that both certolizumab pegol and secukinumab resulted in significantly statistically improvements in health-related quality of life.

**Assessment group's network meta-analysis**

4.8 The committee discussed the results of the network meta-analysis done by the assessment group. It noted that separate analyses were done for each outcome for patients who had had biological therapy, and for patients who had not had biological therapy, to acknowledge the difference in efficacy response in both subpopulations. It also noted that, because of the lack of data, the biological-naive subpopulation (that is, patients who have not had biological therapy before) comprised those patients whose disease had not responded to 1 or more DMARDs. Although it was unclear how many DMARDs patients in the biological-naive subpopulation had previously had, the committee was aware from clinical experts that the efficacy of a biological therapy was not expected

to differ between a patient who has had 1 previous DMARD and a patient who has had 2 previous DMARDs. The committee concluded that the biological-naive subpopulation in the network meta-analysis matched the subpopulation specified in the final NICE scope and it was therefore appropriate to use their data in the cost-effectiveness analysis.

4.9 The committee noted that the assessment group developed several models for use in the cost-effectiveness analysis. These included a model adjusted for 'placebo-creep' (see section 4.6) and exploring the possibility of class effects (adjusted model), as well as a model without any adjustment (independent model). The committee heard from the assessment group and the companies that 'placebo-creep' had been seen in other clinical areas. The committee acknowledged that there was no conclusion on why this occurred. The committee heard from the clinical expert that although ustekinumab (targets IL-12 and IL-23) and secukinumab (targets IL-17A) had a similar clinical pathway, they behaved differently in terms of efficacy and safety and therefore should not be grouped in the same class. The committee heard from the assessment group that adjustment by class reflected any differences in treatment effect within a class. The committee concluded it was reasonable to take into account the adjustment for both 'placebo-creep' and class effect in the analyses.

4.10 The committee noted that the assessment group excluded certolizumab pegol (RAPID-PsA) treatment data from the biological-experienced population network meta-analysis because of the differences in trial eligibility based on the definition of treatment-experienced in PSUMMIT2 (ustekinumab) and FUTURE 2 (secukinumab). In RAPID-PsA, patients whose disease had not responded to a TNF-alpha inhibitor in the first 12 weeks of treatment (see section 4.5) were excluded and only patients whose disease did not respond after 12 weeks, or initially responded but failed to respond thereafter (secondary treatment failure) were included in the biological-experienced subpopulation. In PSUMMIT2 and FUTURE 2,

a mix of patients with early or late primary treatment failure or with secondary treatment failure of a previous TNF-alpha inhibitor were included. The clinical experts agreed that patients with early primary treatment failure would respond differently to a subsequent second biological therapy (that is, TNF-alpha inhibitors). The committee concluded that patients whose disease did not initially respond to a first biological therapy represent a separate subgroup within the overall biological-experienced subpopulation. The committee concluded that it was reasonable for the assessment group to have excluded certolizumab pegol (RAPID-PsA) treatment data from the biological-experienced population network meta-analysis.

4.11 The committee noted that certolizumab pegol and secukinumab showed short-term efficacy in treating psoriatic arthritis compared with placebo. In the biological-naive population, all outcomes showed that certolizumab pegol and secukinumab were effective, but their relative effectiveness compared with etanercept, adalimumab, golimumab and infliximab and with each other, was uncertain, with different treatments being more effective depending on the outcome and analysis (independent and adjusted model). Both certolizumab pegol and secukinumab were consistently more effective than apremilast. The committee noted that the results appeared to show that secukinumab and infliximab are the most effective in terms of PASI response, but this difference was not statistically significant when adjusting for placebo response. In the biological-experienced subpopulation, when only secukinumab 300 mg and ustekinumab were included in the analyses, the results showed that across all outcomes analysed, both secukinumab 300 mg and ustekinumab were statistically significantly more effective than placebo. Most of the outcomes suggested secukinumab 300 mg may be more efficacious than ustekinumab. However, the patient numbers in the biological-experienced subpopulation were quite low; the results were therefore uncertain (with wide overlapping credible intervals). The clinical experts stated that they could not distinguish between the TNF-alpha

inhibitors in improving joint symptoms in clinical practice and would therefore choose 1 of the therapies based on availability and the patient's comorbidities. The committee concluded that although there were limitations in the analyses, it considered that certolizumab pegol and secukinumab were similar to the other therapies in improving joint symptoms in both biological-naive and experienced subpopulations.

**Safety profile**

4.12 The committee heard from the clinical experts that there was no concern about additional adverse events for certolizumab pegol and secukinumab over other biological therapies. The committee concluded that the safety profiles of certolizumab pegol and secukinumab were comparable.

## *Cost effectiveness*

4.13 The committee considered the economic models from the companies and the assessment group. The committee noted that the assessment group updated the York economic model submitted for the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. The update:

- allowed some subgroups to have another active treatment before reverting to best supporting care
- included patients who had initially responded to TNF-alpha inhibitors but whose disease failed to respond thereafter (see section 4.10)
- modelled all subpopulations specified in the NICE scope, as well as patients for whom TNF-alpha inhibitors are contraindicated (subpopulation 4)
- took into account heterogeneity in terms of baseline PASI with results for 3 subgroups within each subpopulation (psoriatic arthritis without concomitant psoriasis, with concomitant mild to moderate psoriasis, with concomitant moderate to severe psoriasis).

The committee concluded that the assessment group's economic model was the most relevant to use for decision-making given its appropriate updates.

**Disease management**

4.14 The committee noted that the assessment group used the same source for disease management costs (specifically health assessment questionnaire costs) as the previous York model (Kobelt et al. 2002) in its base-case analysis. The costs from Kobelt et al. addressed only the arthritis component of psoriatic arthritis, so additional costs were needed to capture the psoriasis element of the disease. The committee noted that another source (Poole et al. 2010) was also considered by the assessment group. Although the study by Poole et al. reported health assessment questionnaire estimates derived from a sample of psoriatic arthritis patients rather than from a sample of rheumatoid arthritis patients (Kobelt et al.), the committee noted the potential limitations of the study, including limited clarity on estimating costs in the model and the total uncertainty surrounding model estimates. The use of the study by Poole et al. was therefore explored as a separate scenario. The committee noted that using the costs from Poole et al. significantly reduces the incremental cost-effectiveness ratios (ICERs) for all treatments relative to best supportive care, although the optimal treatment remained consistent with the base-case analysis across all scenarios. The committee concluded that using the same source as the previous York model was an appropriate choice and its use is consistent across the separate NICE technology appraisals on golimumab and ustekinumab for treating active psoriatic arthritis.

4.15 The committee considered the results of the assessment group's base-case model for 4 subpopulations in line with the proposed positions of certolizumab pegol and secukinumab in the treatment pathway and 3 subgroups according to severity of psoriasis. The committee noted that the assessment group took into consideration the different marketing

authorisations of secukinumab 150 mg and 300 mg according to psoriasis severity (secukinumab 150 mg is licensed for no concomitant psoriasis and mild to moderate psoriasis, secukinumab 300 mg is licensed for moderate to severe psoriasis). Best supportive care is defined as a mix of DMARDs and palliative care.

**Subpopulation 1: 1 previous DMARD but no biological therapy**

4.16 In response to the first appraisal consultation document, Novartis provided additional clinical evidence from FUTURE 2 for subpopulation 1 (people with psoriatic arthritis whose disease had not responded adequately to 1 DMARD). The committee noted that Novartis put the additional clinical evidence into the assessment group's model and generated ICERs comparing secukinumab with best supportive care in all 3 psoriasis subgroups (psoriatic arthritis without concomitant psoriasis, with concomitant mild to moderate psoriasis, with concomitant moderate to severe psoriasis). Although the committee acknowledged that the ICERs were below £20,000 per QALY gained when taking into account the patient access scheme for secukinumab, it identified a number of concerns. The committee heard from the assessment group that the analysis done by Novartis only included secukinumab and best supportive care and therefore was lacking the full comparator set for subpopulation 1, in particular the other biological treatments (etanercept, infliximab, adalimumab and golimumab), which according to their licences could be used in subpopulation 1. Because ICERs are calculated incrementally relative to comparator therapies, without the all appropriate comparators in the analyses, the ICERs presented could misrepresent the true cost effectiveness by a large margin. The committee was aware that comparators included in both the assessment group's model and the additional analysis done by Novartis was to ensure consistency with the NICE scope. It noted that when the scope was written it reflected current treatment at that time (use of biological therapy after 2 DMARDs), but clinical practice may have moved on and the use of biological therapy after 1 DMARD may be becoming more common. However, the

committee was not convinced that the use of biological therapy after 1 DMARD is established clinical practice in the NHS (see section 4.2) and if it is, in which specific group of people it is used. The committee added that given this potential shift in use of biological therapy for psoriatic arthritis, and in particular for new technologies, one of which has a different mechanism of action (see section 4.2), it needed to be very certain about the cost effectiveness of certolizumab pegol and secukinumab in subpopulation 1. The committee recognised that the full sequence of treatments (that is, the treatments a patient has after the first-line treatment) should have been modelled to better capture all the incremental cost and effect differences between the technologies. Without the adequate inclusion of subsequent treatments, the analyses could misrepresent the true ICER. For these reasons, the committee agreed it could not reach a conclusion on the cost effectiveness of certolizumab pegol and secukinumab in subpopulation 1. It also acknowledged the previous discussion that, in clinical practice, TNF-alpha inhibitors are usually used after adequate trials of 2 DMARDs (see section 4.2). The committee concluded it was unable to recommend certolizumab pegol and secukinumab as treatment options for people with psoriatic arthritis whose disease had not responded adequately to 1 DMARD.

**Subpopulation 2: at least 2 previous DMARDs and no biological therapy**

4.17 The committee considered that in all psoriasis subgroups, certolizumab pegol and secukinumab 150 mg and 300 mg were cost effective compared with best supportive care, when taking into account the patient access scheme for both therapies. ICERs for both strengths of secukinumab were less than £20,000 per QALY gained compared with best supportive care. For certolizumab pegol, the ICERs were close to, or less than £20,000 per QALY gained compared with best supportive care. The committee considered that the cost effectiveness for certolizumab pegol and secukinumab was acceptable when the criteria in etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis are met;

that is, the person has peripheral arthritis with at least 3 tender joints and at least 3 swollen joints, and the psoriatic arthritis has not responded to adequate trials of at least 2 standard DMARDs, given either individually or in combination. The committee therefore concluded that certolizumab pegol and secukinumab could be recommended as treatment options for people with psoriatic arthritis if used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.

**Subpopulation 3: patients who have had biological therapies**

4.18 The committee noted that secukinumab 300 mg was considered as a relevant intervention, alongside ustekinumab and best supportive care, in patients who have had biological therapy. Certolizumab pegol was not included in subpopulation 3 because only patients whose disease had initially responded to a biological treatment and stopped responding thereafter were included in the RAPID-PsA trial (see section 4.10). The committee considered that secukinumab 300 mg was cost effective in patients who had had biological therapy (including primary and secondary treatment failures) with ICER values below, or close to, £20,000 per QALY gained compared with best supportive care, when taking into account the patient access scheme for secukinumab 300 mg. The committee therefore concluded that secukinumab 300 mg could be recommended as a treatment option for people with psoriatic arthritis whose disease has not responded adequately to 2 DMARDs and has not responded to a TNF-alpha inhibitor within the first 12 weeks or has stopped responding after 12 weeks and only when taking into account the patient access scheme for secukinumab 300 mg.

4.19 The committee noted the assessment group did a separate cost-effectiveness analysis (as part of the scenario analysis) for patients whose disease has stopped responding to a TNF-alpha inhibitor after the first 12 weeks. It was aware that, in the absence of data for other comparators for this subgroup, the comparison is restricted to certolizumab pegol and

best supportive care. The committee noted that for certolizumab pegol compared with best supportive care, the ICERs were below, or very close to, £20,000 per QALY gained, when taking into account the patient access scheme for certolizumab pegol. The committee therefore concluded that certolizumab pegol could be recommended as a treatment option for people with psoriatic arthritis whose disease has not responded adequately to 2 DMARDs and whose disease has stopped responding to a TNF-alpha inhibitor after the first 12 weeks, and only when taking into account the patient access scheme.

### Subpopulation 4: patients in whom TNF-alpha inhibitors are contraindicated

4.20 The committee noted that secukinumab was compared with ustekinumab and best supportive care. It noted that certolizumab pegol was not included because it was assumed that other TNF-alpha inhibitors including certolizumab pegol would be contraindicated in these patients. In the absence of effectiveness data for these patients, the analysis was done using data from the biological-naive populations from the secukinumab and ustekinumab trial. The committee heard from clinical experts that this was considered a reasonable approach. The committee noted that the assessment group considered the different licensed strengths of secukinumab 150 mg and 300 mg according to psoriasis severity (see section 4.16). The committee noted that secukinumab 150 mg and 300 mg compared with best supportive care resulted in ICERs below £20,000 per QALY gained in patients without concomitant psoriasis, with mild to moderate psoriasis and with moderate to severe psoriasis, when taking into account the patient access scheme for secukinumab. The committee therefore concluded that secukinumab could be recommended as a treatment option for people with psoriatic arthritis in whom TNF-alpha inhibitors are contraindicated but would otherwise be considered, and only when taking into account the patient access scheme for secukinumab.

4.21 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 12 weeks and 16 weeks stop treatment with certolizumab pegol and secukinumab, respectively. The committee considered that the recommendation to stop treatment based on an inadequate PsARC response (as defined in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis) was also appropriate for certolizumab pegol and secukinumab (assessed at 12 weeks and 16 weeks respectively). 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.

### *Innovation*

4.22 The committee noted the convenience of self-administration. It concluded that secukinumab and certolizumab pegol are important treatments and represent additional options for patients with active psoriatic arthritis that has not responded to prior DMARDs. It was aware of its earlier conclusion that although UCB provided evidence of certolizumab pegol's impact on pain and fatigue, it was not possible to determine the impact of any potential adjustment on the QALY because the assessment group's modelling involved mapping from the health assessment questionnaire and PASI to a utility score (see section 4.7). It noted that if health benefits have been missed, this would apply across all the interventions and comparators. Therefore the committee concluded that there were no other significant health benefits that had not been captured in the cost-effectiveness model.

## *Summary of appraisal committee's key conclusions*

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| | **psoriatic arthritis after inadequate response to DMARDs** | |
| **Key conclusion** | | |
| Certolizumab pegol alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:<br>• it is used as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or<br>• the person has had a TNF-alpha inhibitor but their disease has stopped responding after the first 12 weeks.<br>Certolizumab pegol is only recommended if the company provides it as agreed in the patient access scheme. | | 1.1 |
| Secukinumab alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:<br>• it is used as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or<br>• the person has had a TNF-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks or<br>• TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, | | 1.2 |

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| infliximab and adalimumab for the treatment of psoriatic arthritis).<br><br>Secukinumab is only recommended if the company provides it with the discount agreed in the patient access scheme.<br><br>For subpopulation 1 (1 previous disease-modifying antirheumatic drug [DMARD] but no biological therapy), the committee was aware that comparators included in both the assessment group's analysis and the additional analysis done by Novartis was to ensure consistency with the NICE scope. It noted that, when the scope was written, it reflected current treatment at the time (use of biological therapy after 2 DMARDs), but clinical practice may have moved on and use of biological therapy after 1 DMARD may be becoming more common. However, the committee was not convinced that the use of biological therapy after 1 DMARD is established clinical practice in the NHS, and if it is, in which specificgroup of people it is used. The committee added that given the potential shift in clinical practice for psoriatic arthritis, it needed to be very certain about the cost effectiveness of certolizumab pegol and secukinumab in subpopulation 1. The committee added that given this potential shift in use of biological therapy for psoriatic arthritis, and in particular for new technologies, one of which has a different mechanism of action (see section 4.2), it needed to be very certain about the cost effectiveness of certolizumab pegol and secukinumab in subpopulation 1. The committee recognised that the full sequence of treatments (that is, the treatments a patient has after the first-line treatment) should have been modelled to better capture all the incremental cost and effect differences between the technologies. Without the adequate inclusion of subsequent treatments, the analyses could misrepresent the true ICER. For these reasons, the committee | 4.16 |

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| agreed it could not reach a conclusion on the cost effectiveness of certolizumab pegol and secukinumab in subpopulation 1. It also acknowledged the previous discussion that, in clinical practice, TNF-alpha inhibitors are usually used after adequate trials of 2 DMARDs | |
| For subpopulation 2 (at least 2 previous DMARDs and no biological therapy), the committee noted that, in all psoriasis subgroups, certolizumab pegol and secukinumab 150 mg and 300 mg were cost effective compared with best supportive care, when taking into account the patient access scheme for both therapies. Incremental cost-effectiveness ratios (ICERs) for both strengths of secukinumab were less than £20,000 per quality-adjusted life year (QALY) gained compared with best supportive care. For certolizumab pegol, the ICERs were close to, or less than £20,000 per QALY gained compared with best supportive care. The committee therefore concluded that certolizumab pegol and secukinumab could be recommended as treatment options for people with psoriatic arthritis if used as described for the TNF-alpha inhibitors in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. | 4.17 |
| For subpopulation 3 (patients who have had biological therapies), the committee reviewed 2 subgroups:<br>• People with psoriatic arthritis whose disease has not responded adequately to 2 DMARDs and has not responded to TNF-alpha inhibitors within the first 12 weeks or has stopped responding after 12 weeks; the committee noted that secukinumab 300 mg was cost effective compared with best supportive care. ICERs were below, or close to, £20,000 per QALY gained, when taking into account the | 4.18, 4.19 |

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| patient access scheme for secukinumab 300 mg. The committee concluded that secukinumab 300 mg could be recommended as a treatment option in this patient population only when taking into account the patient access scheme for secukinumab 300mg.<br><br>• People with psoriatic arthritis whose disease has not responded adequately to 2 DMARDs and whose disease has not responded adequately to DMARDs and whose disease has stopped responding to TNF-alpha inhibitors after the first 12 weeks; the committee noted that certolizumab pegol was cost effective compared with best supportive care with ICERs below or very close to £20,000 per QALY gained, when taking into account the patient access scheme for certolizumab pegol.<br><br>For subpopulation 4 (patients in whom TNF-alpha inhibitors are contraindicated), the committee noted that secukinumab 150 mg and 300 mg compared with best supportive care resulted in ICERs below £20,000 per QALY gained in all psoriasis subgroups, when taking into account the patient access scheme for secukinumab. The committee concluded that secukinumab could be recommended as a treatment option for people with psoriatic arthritis in whom TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis), and only when taking into account the patient access scheme for secukinumab. | 4.20 |
| **Current practice** | |
| Clinical need of patients, including the availability of | The committee recognised the importance to patients and clinical experts of addressing the associated comorbidities, | 4.1, 4.2 |

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| alternative treatments | which are not always captured in current research. It also heard that response to treatment is heterogeneous in terms of efficacy and safety. Therefore there is a clinical need for alternative therapies in the treatment pathway to offer more options, particularly in people with active psoriatic arthritis whose disease has responded inadequately to previous DMARD therapies. | |
| **The technologies** | | |
| Proposed benefits of the technology/ies<br><br>How innovative is the technology/are the technologies in its/their potential to make a significant and substantial impact on health-related benefits? | The committee heard from the clinical experts that secukinumab has a different mechanism of action, which could potentially benefit people in whom TNF-alpha inhibitors are contraindicated or not tolerated. The committee noted the convenience of self-administration for certolizumab pegol and secukinumab. It concluded that there were no other significant health benefits that had not been captured in the cost-effectiveness model. | 4.2, 4.22 |
| What is the position of the treatments in the pathway of care for the condition? | The treatments are for:<br><br>• people whose disease has responded inadequately to at least 2 DMARDs, in line with guidelines from the British Society for Rheumatology and the European League Against Rheumatism, and NICE technology appraisal guidance on etanercept, infliximab and | 4.2 |

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| | adalimumab for the treatment of psoriatic arthritis<br><br>• people with psoriatic arthritis whose disease has not responded adequately to at least 2 DMARDs and TNF-alpha inhibitors within the first 12 weeks or has stopped responding after 12 weeks<br><br>• people with psoriatic arthritis whose disease has not responded to at least 2 DMARDs and has stopped responding to TNF-alpha inhibitor after the first 12 weeks<br><br>• people in whom TNF-alpha inhibitors are contraindicated. | 4.18<br><br>4.19<br><br>4.20 |
| Adverse reactions | The committee heard from the clinical experts that there was no concern about additional adverse events for certolizumab pegol and secukinumab over other biological therapies. | 4.12 |
| **Evidence for clinical effectiveness** | | |
| Availability, nature and quality of evidence | The committee noted that the main sources of evidence were RAPID-PsA (certolizumab pegol) and FUTURE 2 (secukinumab). The trials compared a biological therapy (and apremilast) with placebo. The committee considered that both trials were of good quality and had a reasonably low risk of bias. | 4.3, 4.4 |

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| | The committee considered the results of the network meta-analysis done by the assessment group. It noted that separate analyses were done for each outcome for patients who had had biological therapy, and for patients who had not had biological therapy to acknowledge the difference in efficacy response in both subpopulations. | 4.8 |

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| Relevance to general clinical practice in the NHS | There were no direct head-to-head trials with treatments currently used in the NHS.<br><br>The committee concluded that the biological-naive subpopulation in the network meta-analysis matched the subpopulation specified in the final NICE scope and it was therefore appropriate to use their data in the cost-effectiveness analysis.<br><br>In RAPID-PsA, patients whose disease had not responded to a TNF-alpha inhibitor in the first 12 weeks of treatment were excluded and only patients whose disease did not respond after 12 weeks, or initially responded but failed to respond thereafter (secondary treatment failure) were included in the biological-experienced subpopulation. The committee concluded that patients whose disease did not initially respond to a first biological therapy represent a separate subgroup within the overall biologic-experienced subpopulation. The committee concluded that it was reasonable for the assessment group to have excluded certolizumab pegol (RAPID-PsA) treatment data from the biological-experienced population network meta-analysis.<br><br>The committee noted that populations recruited in clinical trials have changed | 4.8<br><br>4.10<br><br>4.6 |

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| | over time, with earlier trials excluding patients who had previously had biological therapies and later trials including such patients. | |

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| Uncertainties generated by the evidence | Placebo response rates have increased markedly over time across the trials, referred to as 'placebo-creep'. The committee concluded it was reasonable to take into account the adjustment for both 'placebo-creep' and class effect.<br><br>The committee concluded that because these issues had either not been accounted for (secukinumab) or because it was unclear how they had been accounted for (certolizumab pegol) in the company submissions, it was not possible to make reliable conclusions about the difference in the efficacy of certolizumab pegol and secukinumab using the companies' analyses. | 4.6, 4.9<br><br>4.6 |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | See 'What is the position of the treatments in the pathway of care for the condition?' | – |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The committee concluded that although there were limitations in the analyses, it considered that certolizumab pegol and secukinumab were similar to the other therapies in improving joint symptoms in both biological-naive and experienced subpopulations. | 4.11 |

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| | The committee noted that treatment with certolizumab pegol and secukinumab resulted in statistically significant improvements in health-related quality-of-life measures and in improvements in extra-articular manifestations such dactylitis (that is, inflammation of the fingers or toes) and enthesitis (that is, inflammation of tendons or ligaments). | 4.7 |
| **Evidence for cost effectiveness** | | |
| Availability and nature of evidence | the committee was aware that comparators included in both the assessment group's analysis and the additional analysis done by Novartis was to ensure consistency with the NICE scope. It noted that, when the scope was written, it reflected current treatment at the time (use of biological therapy after 2 DMARDs), but clinical practice may have moved on and use of biological therapy after 1 DMARD may be becoming more common. However, the committee was not convinced that the use of biological therapy after 1 DMARD is established clinical practice in the NHS, and if it is, in which specificgroup of people it is used. The committee added that given the potential shift in clinical practice for psoriatic arthritis, it needed to be very certain about the cost effectiveness of certolizumab pegol and secukinumab in subpopulation 1. The committee added that | 4.16 |

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| | given this potential shift in use of biological therapy for psoriatic arthritis, and in particular for new technologies, one of which has a different mechanism of action, it needed to be very certain about the cost effectiveness of certolizumab pegol and secukinumab in subpopulation 1. The committee recognised that the full sequence of treatments (that is, the treatments a patient has after the first-line treatment) should have been modelled to better capture all the incremental cost and effect differences between the technologies. Without the adequate inclusion of subsequent treatments, the analyses could misrepresent the true ICER.<br><br>The committee concluded that the biological-naive subpopulation in the network meta-analysis matched the subpopulation specified in the final NICE scope and it was therefore appropriate to use their data in the cost-effectiveness analysis. | 4.8 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | Although the committee acknowledged that the ICERs were below £20,000 per QALY gained when taking into account the patient access scheme for secukinumab, it identified a number of concerns. | 4.16 |

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| Incorporation of health-related quality-of-life benefits and utility values<br><br>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered? | No other health-related benefits have been identified that have not been captured in the QALY calculation. | 4.22 |
| Are there specific groups of people for whom the technology/ies is/are particularly cost effective? | The committee considered the results of the assessment group's base-case model for 4 subpopulations in line with the proposed positions of certolizumab pegol and secukinumab in the treatment pathway and 3 subgroups according to severity of psoriasis. | 4.16 to 4.20 |
| What are the key drivers of cost effectiveness? | The committee noted that the use of a different source of disease management costs impacted significantly on the ICERs for all treatments relative to best supportive care, although the optimal treatment remained consistent with the base-case analysis across all scenarios. | 4.14 |
| Most likely cost-effectiveness | The committee concluded that certolizumab pegol is cost effective in 2 subpopulations (patients who had at least 2 previous | 4.17, 4.18, 4.19 |

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| estimate (given as an ICER) | DMARDs and no biological therapy, and patients who have had TNF-alpha inhibitors whose disease has stopped responding to TNF-alpha inhibitor after the first 12 weeks) with ICERs below, or close to, £20,000 per QALY gained when taking into account the proposed patient access scheme for certolizumab pegol.<br><br>The committee concluded that secukinumab is cost effective in 3 subpopulations (patients who had at least 2 previous DMARDs and no biological therapy, and patients who have had TNF-alpha inhibitors whose disease has not responded to TNF-alpha inhibitors within the first 12 weeks or has stopped responding after 12 weeks, and patients in whom TNF-alpha inhibitors are contraindicated) with ICERs below, or close to, £20,000 per QALY gained only when taking into account the patient access scheme for secukinumab. | 4.17, 4.18, 4.20 |
| **Additional factors taken into account** | | |
| Patient access schemes (PPRS) | Patient access schemes were taken into account for certolizumab pegol, golimumab, ustekinumab and secukinumab. | – |
| End-of-life considerations | Not applicable | – |

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| Equalities considerations and social value judgements | The committee noted that some people may have physical, sensory or learning disabilities or communication difficulties that could affect their responses to components of the Psoriatic Arthritis Response Criteria (PsARC), and concluded that healthcare professionals should take this into account when using the PsARC. | 4.21 |

# 5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

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 active psoriatic arthritis and the doctor responsible for their care thinks that certolizumab pegol or secukinumab are the right treatments, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Novartis have agreed that secukinumab will be available to the NHS with a patient access scheme which makes it available with a discount. The Department of Health and UCB have agreed that a patient access scheme for certolizumab pegol which provides a rebate to the list price of certolizumab pegol, applied at the point of purchase or invoice. The NHS will not pay for certolizumab pegol for the first 12 weeks. The size of these discounts is commercial in confidence. It is the responsibility of the companies to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme for secukinumab should be directed to [NICE to add details at time of publication] and for certolizumab pegol should be directed to

# 6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Lindsay Smith
Vice-Chair, appraisal committee
December 2016

# 7 Appraisal committee members and NICE project team

## *Appraisal committee members*

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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.

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.

## *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.

**Aminata Thiam**
Technical Lead

**Fay McCracken**
Technical Adviser

**Kate Moore**
Project Manager

ISBN: [to be added at publication]