

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Apremilast for treating active psoriatic arthritis

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using apremilast in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and 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 draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (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 provisional 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 this technology.
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 apremilast in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 10th July 2015

Second Appraisal Committee meeting: 22nd July 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

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1 Appraisal Committee's preliminary recommendations

- 1.1 Apremilast alone or in combination with disease-modifying antirheumatic drug (DMARD) therapy is not recommended within its marketing authorisation for treating adults with active psoriatic arthritis that has not responded to prior DMARD therapy, or such therapy is not tolerated.
- 1.2 People whose treatment with apremilast was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Apremilast (Otezla, Celgene) is a small-molecule inhibitor of phosphodiesterase 4 (PDE4). Apremilast down-regulates the inflammatory response by modulating the expression of inflammatory and anti-inflammatory cytokines and mediators associated with psoriatic arthritis (including tumour necrosis factor [TNF]-alpha and interleukin [IL]-23). Its UK marketing authorisation states that apremilast 'alone or in combination with disease-modifying antirheumatic drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy'.

- 2.2 The summary of product characteristics includes the following adverse reactions for apremilast: gastrointestinal (GI) disorders (most commonly diarrhoea and nausea); upper respiratory tract infections; headache; and tension headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 Apremilast is an oral tablet. The recommended dosage is 30 mg twice daily after an initial titration schedule. A single 10 mg dose is given on the first day of treatment; this is titrated to 30 mg twice daily over 5 days (see the summary of product characteristics for the dose titration schedule). The price of apremilast is £265.18 for a 14-day treatment initiation pack (4×10 mg tablet; 4×20 mg tablet; 19×30 mg tablet) and £550.00 for a 28-day-treatment standard pack (56×30 mg) (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] online accessed March 2015). The cost of 12 months of treatment with apremilast is estimated at £7140.18 (company submission). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

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

Clinical effectiveness

- 3.1 The company's submission included 3 international, multicentre, randomised, double-blind, placebo-controlled trials, that were almost identical in design (n=1493): PSA-002 (also known as PALACE 1), PSA-003 (PALACE 2) and PSA-004 (PALACE 3). The trials included adults with active psoriatic arthritis (3 or more swollen and tender joints for at least 6 months) who previously had

treatment with conventional disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) alpha inhibitors (PASI-004 also included patients with at least 1 psoriasis lesion, of at least 2 cm, which had not responded adequately to conventional DMARDs). The baseline characteristics were very similar across the randomised groups in the 3 trials. An analysis of pooled data from the 3 trials was included in the company submission.

- 3.2 Each trial had a planned duration of 5 years and consisted of 2 treatment phases: an initial 24-week double-blinded, placebo-controlled phase and a 236-week (4.5 years) active treatment/long-term safety phase. At week 16, all people in the placebo group whose disease had not shown improvement (that is, whose swollen joint count and tender joint count had not improved by at least 20% from baseline) crossed over to blinded active treatment (randomised to either 20 mg or 30 mg apremilast). Those already having apremilast whose disease did not improve, remained on the same dose of apremilast. At week 24, people having placebo were re-randomised to have apremilast.
- 3.3 The 3 trials collected measures of health-related quality of life using: the Health Assessment Questionnaire Disability Index (HAQ-DI); the SF-36v2 survey; EQ-5D; the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Medical Outcomes Study (MOS) sleep scale; and the work limitations questionnaire (WLQ).
- 3.4 The primary outcome in all 3 trials was the American College of Rheumatology response criteria (ACR20 response) at week 16. The major secondary outcome was the change from baseline to week 16 in the HAQ-DI score and the modified Psoriasis Arthritis Response Criteria (PsARC) response, and a 75% reduction in the Psoriasis Area Severity Index (PASI-75 response). Other outcomes

included: tender joint count and swollen joint count; SF-36v2 PF domain scores; pain visual analogue scores; Maastricht Ankylosing Spondylitis Enthesitis Score (MASES); dactylitis severity scores; 28-joint Disease Activity Score (DAS28) using C-reactive protein (CRP) as an acute phase reactant; FACIT-fatigue scale; the European League Against Rheumatism (EULAR) response; ACR50; ACR70; and the Clinical Disease Activity Index (CDAI). Data were collected at weeks 16, 24 and 52. The 3 exploratory endpoints were PASI-75, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score and American College of Rheumatology (ACR-N) index. Follow-up data were included for up to 104 weeks for PSA-002 and up to 52 weeks for PSA-003 and PSA-004.

- 3.5 The company presented pooled analyses of the 3 trials which showed that, compared with placebo, apremilast was associated with statistically significant improvements in the proportion of people who had an ACR20 response. The size of the treatment benefit was modest, with an ACR20 response experienced by 37% of people having apremilast compared with 19% having placebo ($p \leq 0.0001$). Apremilast, compared with placebo, was also associated with statistically significant improvements in the proportion of people experiencing an ACR50 response (13.9% and 6.5%, respectively; $p \leq 0.0001$), PsARC response (49% and 30%, respectively; $p \leq 0.0001$) and minimal clinically important difference (MCID) of equal to, or more than, 0.30 in the HAQ-DI score (36.4% and 26%, respectively; $p \leq 0.001$). No statistically significant difference was shown for ACR70 response or enthesitis score.
- 3.6 In the 30 mg apremilast group and the placebo group, 221 and 205 people, respectively, had dactylitis. The dactylitis count at baseline was 3.3 (standard deviation [SD] 3.26) in the 30 mg apremilast

group and 3.2 (SD 3.29) in the placebo group. The reduction in dactylitis at both week 16 and 24 was greater in the 30 mg apremilast group than in the placebo group (-1.7 [standard error; SE 0.17] compared with -1.3 [SE 0.18], p=0.0485; and 1.8 [SE 0.16] compared with -1.2 [SE 0.17], p=0.0097 respectively). At week 52, 65.9% of people with pre-existing dactylitis no longer had the condition on their hands or feet compared with 43.1% at week 16.

- 3.7 In the pooled analysis, 249 people in the 30 mg apremilast group and 231 people in the placebo group had at least 3% of their body surface area affected by psoriasis at week 16 and were therefore evaluated for a PASI-75 response. A greater proportion of people in the apremilast group than in the placebo group achieved a PASI-75 response at week 16 (22.1% compared with 5.2%, p<0.0001). At week 52, 38.3% of people had a PASI-75 response. The company noted that the pooled population had low baseline PASI scores making the PASI scale less sensitive to change and possibly underestimating the magnitude of improvement.
- 3.8 As there were no head-to-head trials comparing apremilast with all of the relevant comparators, the company carried out a systematic review and a network meta-analysis using a Bayesian analysis framework. The company considered the treatments of interest in the network meta-analysis to be apremilast, adalimumab, etanercept, golimumab and infliximab. However, following a clarification request from the Evidence Review Group (ERG) for a more comprehensive set of analyses, updated network meta-analyses were presented. These included 19 studies that compared apremilast with adalimumab, etanercept, golimumab, infliximab, certolizumab pegol and ustekinumab. The efficacy outcome endpoints in the included trials ranged from 12–16 weeks.

These analyses were carried out for the whole population and also for the TNF-alpha inhibitor naive subgroup. The deviance information criterion (DIC) slightly favoured the fixed-effect model so that was selected for all outcomes, except HAQ-DI for which a random-effects model was selected. The efficacy outcome endpoints in the included trials ranged from 12–16 weeks. These analyses were carried out for the whole population and also for the TNF-alpha inhibitor naive subgroup.

- 3.9 The highest probabilities of PsARC response were seen with golimumab 50 mg followed by golimumab 100 mg and infliximab 5 mg/kg. Probability of PsARC response with apremilast (marked as ‘academic in confidence’ by the company) was lower than all of the other active treatments. The odds ratios for these treatments were also calculated relative to placebo and all treatments except apremilast resulted in an odds ratio of greater than 1. The company validated the PsARC result using data from Rodgers et al., 2011.
- 3.10 The highest probability of response for ACR20, 50 and 70 was seen with infliximab 5 mg/kg. Apremilast had a lower probability of response than all of the other active treatments. The highest probability of response for all of the PASI outcomes was also seen with infliximab 5 mg/kg. Apremilast had a higher probability of response compared with placebo and a similar probability of response compared with etanercept.
- 3.11 When comparing active treatments with placebo, large reductions in HAQ-DI were seen after treatment with infliximab and etanercept. The smallest reduction was seen after treatment with apremilast. Reductions in HAQ-DI were larger in people who had a PsARC response than in those who did not.

- 3.12 The company did a subgroup analysis for people who had not had TNF-alpha inhibitor treatment. This was not a predefined subgroup in the trials. Outcomes for ACR20, 50 and 70, PASI, PsARC and HAQ-DI were calculated during the network meta-analyses. The data showed the effect of apremilast to be consistent with the treatment benefit observed for the whole population. The ERG noted discrepancies in several of the efficacy results for the subgroup of people who had not had TNF-alpha inhibitor treatment.
- 3.13 Adverse events were not a primary outcome in any of the trials but the trials did record serious adverse events, severe adverse events and adverse events leading to discontinuation from treatment. The company's submission presented data from the pooled analysis of all 3 trials which showed that treatment-related adverse events were almost double in the apremilast 30 mg group compared with the placebo group; 189 (38.0%) and 92 (18.6%), respectively. Adverse events did not lead to deaths in either group but did lead to discontinuation of treatment; 36 people (7.2%) in the apremilast group and 21 people (4.2%) in the placebo group. The adverse events decreased between weeks 0, 24 and 52.

Cost effectiveness

- 3.14 The company developed a Markov model with a 28-day cycle length (to account for the 12- and 16-week treatment trial periods) and 40-year time horizon. The company did not apply half-cycle correction to the model because it considered the cycle to be sufficiently short. The treatment responses in the model were considered as mutually exclusive health states, with response to treatment evaluated at the end of a treatment period according to PsARC and PASI 75 criteria. The model compared treatment sequences including and excluding apremilast. If a person's disease did not respond they were counted as a 'non-responder'

and moved to the next treatment option in the pathway. ‘Responders’ continued treatment until they experienced lack of efficacy or adverse events. Adverse events were not explicitly modelled but were implicitly included because of the effect on initial response and withdrawal from treatment. A discount rate of 3.5% was applied for costs and outcomes, and the analysis was from the NHS and personal social services perspective.

- 3.15 Each treatment in the company’s model consisted of 2 possible health states: trial period (that is, response period) and continued use (that is, maintenance). The response to treatment (with apremilast or TNF-alpha inhibitors) was evaluated at the end of each treatment-specific trial period according to PsARC criteria (at 16 weeks for apremilast, in line with the trials, and at 12 weeks for the TNF-alpha inhibitors, in line with previous other NICE psoriatic arthritis appraisals). At the end of the trial period people whose disease responded to treatment were assumed to continue treatment until they stopped because of lack of efficacy (‘secondary non-responders’) or other causes, based on an annual all-inclusive long-term withdrawal rate. People whose disease did not respond to treatment moved to the next treatment option in the sequence.
- 3.16 The transition probabilities for both the response and maintenance periods were determined by the PsARC response criteria, calculated from the company’s network meta-analysis. In the base case analysis, the short- and long-term efficacy (PsARC rates and long-term withdrawal rates) for the TNF-alpha inhibitors were reduced for primary non-responders. This was because of a likely reduction in the efficacy of TNF-alpha inhibitors if used at subsequent lines of treatment. No efficacy reduction was applied to secondary non-responders to TNF-alpha inhibitors. For people whose condition did not respond to an initial therapy, but that did

respond to a subsequent TNF-alpha inhibitor therapy, the loss of efficacy was applied for the proportion of people who stopped treatment due to loss of efficacy (a hazard ratio [HR] of 2.7). The company assumed that apremilast would not affect the efficacy of subsequent TNF-alpha inhibitor treatments and therefore no change in efficacy was necessary. It was assumed that the withdrawal rate was constant over time for all treatments (16.5%), taking into account loss of initial response and withdrawal due to adverse events and that the rate was the same for all the TNF-alpha inhibitors and apremilast.

- 3.17 Trials PSA -002, PSA -003 and PSA -004 collected EQ-5D data at baseline and at week 16, but the company noted that these data were not available for all of the TNF-alpha inhibitors included in its analysis. Utility values for the health states were therefore modelled using the correlation coefficient between the PsARC scores and PASI scores (measuring skin disease response) using a previously published regression equation based on data from the ADEPT trial (correlation coefficient 0.436) (Rodgers et al. 2011). The values were assumed to be unchanged until the person's condition no longer responded to treatment (non-responder). A key assumption in the model was that people whose condition continued to respond to treatment at the end of the trial period remained with the same HAQ-DI score. PASI was included in the health states to account for the impact of psoriasis on the quality of life of people with psoriatic arthritis. When the person's psoriatic arthritis stopped responding to treatment they were assumed to become 'non-responders' and were assigned a greater HAQ-DI score. Changes in HAQ-DI scores for PsARC responders and non-responders were treatment specific. People who reached best supportive care were assumed to experience subsequent natural progression of their disease, resulting in an increase (worsening) in HAQ-DI score of

- 0.006 per 28 days over time, up to a maximum score of 3, based on Rodgers et al. 2011. The death health state captured age-related mortality.
- 3.18 In the model, adverse events were only considered in terms of the effects on initial response (responders could stop treatment because of adverse events) and on the long-term discontinuation and withdrawal rates from each treatment option.
- 3.19 The company's base case incremental cost-effectiveness ratio (ICER) for the comparison of the apremilast treatment sequence (apremilast followed by adalimumab, etanercept and best supportive care) compared with the comparator treatment sequence (adalimumab followed by etanercept and best supportive care) was £14,691 per quality-adjusted life year (QALY). The company provided updated analyses after the ERG noted differences between the efficacy inputs used in the company's model and those included in its written submission. The updated ICER for the same comparison was £14,683 per QALY gained.
- 3.20 The company provided a direct displacement scenario in which apremilast replaced a biologic in the treatment pathway, with apremilast being positioned as the first treatment in the apremilast sequences. In the scenario for apremilast then etanercept then best supportive care, compared with adalimumab then etanercept then best supportive care, the apremilast sequence was dominant (it cost less and was at least as effective as the comparator sequence). In the displacement scenario for apremilast then etanercept then golimumab then best supportive care, compared with adalimumab then etanercept then golimumab then best supportive care, the ICER was £2,568 per QALY gained.

- 3.21 The company provided an additional scenario in which there was no effect on the HAQ-DI progression for apremilast when patients remained on treatment. This produced an ICER of £22,868 per QALY gained.
- 3.22 The company also provided scenario analyses incorporating the placebo response in the best supportive care group, with the following assumptions:
- PsARC placebo response rates were used to identify patients who spontaneously achieved response in best supportive care
 - a constant utility was assumed based on the placebo HAQ-DI change from baseline in PsARC responders (-0.256)
 - the PASI 50, PASI 75 and PASI 90 placebo response rates were 15.15%, 5.638% and 1.25%, respectively
 - patients who did not experience a placebo response in best supportive care were assigned the same utilities and costs as in the base-case analysis.

This resulted in an ICER of £22,349 per QALY gained.

- 3.23 The company presented the life years spent on each treatment option for each sequence. When apremilast was added to the treatment sequence, the time spent on TNF-alpha inhibitors and best supportive care was reduced compared with the comparator sequence and the PsARC and PASI-75 responses increased. The sequences did not affect mortality so total life years did not change. There was a QALY increase (incremental of 0.74) for people having the apremilast sequence primarily because they spent less time on best supportive care, although there was also a gain in duration response.

- 3.24 The company did a subgroup analysis for people who had not had TNF-alpha-inhibitor treatment, by excluding patients who had previously had biologic therapies. The company applied PsARC response rates in the model, which were taken from the network meta-analysis based on people who had not had TNF-alpha-inhibitor treatment. The resulting ICER was £14,697 per QALY gained.
- 3.25 The company carried out 1-way deterministic sensitivity analyses on inputs used in the base case analysis, to determine the impact on the ICER. It stated that the cost-effectiveness was mainly driven by the benefits associated with a delay in progression to, and a reduction in time spent, being treated with (more costly) injectable TNF-alpha inhibitors and in best supportive care. The HAQ-DI score was varied between 0.001 and 0.011 which resulted in ICERs of £37,881 and £11,604 per QALY gained, respectively, for the comparison of the apremilast sequence with the base case comparison sequence.
- 3.26 The company also carried out probabilistic sensitivity analyses by running 5000 simulations. This concluded that the probability that the apremilast sequence is cost-effective compared with the base case comparator sequence is 0.81 at a willingness-to-pay threshold of £20,000 per QALY gained, and 0.94 at a willingness-to-pay threshold of £30,000 per QALY gained. The probabilistic base case results were similar to the deterministic results (£14,700 per QALY gained compared with £14,683 per QALY gained, respectively), which suggested that there were no issues regarding the non-linearity of the model.
- 3.27 The company modelled 14 scenarios to assess the uncertainty of the model:

- Number of TNF-alpha inhibitor options in the treatment sequence.

The per-patient QALY gained from the addition of apremilast before adalimumab (in the sequence apremilast then adalimumab then best supportive care) was significantly higher than in the base case, with an average of 0.92 QALYs gained in the apremilast sequence compared with the comparator sequence (adalimumab then best supportive care); almost 1 year in perfect health per patient at the net present value over a time horizon of 40 years. The resulting ICER was £14,636 per QALY gained. When comparing the sequences of 2 TNF-alpha inhibitors with and without apremilast, the resulting cost per QALY gained was £14,737.

- Alternative positioning of apremilast in the treatment sequence.

If apremilast was placed after TNF-alpha inhibitors in the sequence the treatment cost was more but was associated with a greater number of QALYs. The estimated saving achieved by positioning apremilast before TNF-alpha inhibitors in the treatment sequence was £13,14 per patient, with a negligible reduction of 0.05 QALYs over a 40-year time horizon. The resulting ICER was £24,470 saved per QALY lost.

- Reduced TNF-alpha inhibitor efficacy after a primary non-response to at least 1 TNF-alpha inhibitor.

This caused a marginal impact on the ICER with an increase to £14,752 per QALY gained compared with the base case.

- Reduced TNF-alpha inhibitor efficacy after non-response to apremilast.

The company assumed that non-response to apremilast led to a 5% reduction in the probability of PsARC and PASI responses to the following treatment option. In the apremilast treatment sequence, the reduction in efficacy of the first TNF-alpha

inhibitor resulted in lower costs and QALYs. The costs were lower per patient because a higher proportion of disease did not show a primary response and therefore people were moved to the next treatment option. The ICER for this scenario was estimated to be £14,457 per QALY gained.

- Response to therapy and discontinuation rules.

Response to therapy was defined as the achievement of at least one of either a PsARC or PASI-75 response. Compared with the base case, both treatment sequences resulted in higher average costs and QALYs per patient. The ICER increased slightly to £14,702 per QALY gained.

- Time horizon.

Model outcomes were evaluated using 3 different time horizons: 1, 5 and 10 years. Over the 1-year time horizon the differential costs were negative with apremilast resulting in a saving of £292 per patient with 0.03 QALYs lost per patient. For a 5-year time horizon, people had best supportive care for 0.87 or 1.51 patient years for the apremilast and comparator sequence, respectively. This time horizon resulted in an ICER of £111,552 per QALY gained, with an expected additional cost of £1777 per patient for a negligible average gain of 0.02 QALYs. The ICER for the 10-year time horizon was £33,442 per QALY gained with 1.39 fewer patient-years spent receiving best supportive care and 1.22 fewer patient-years spent on TNF-alpha inhibitors when comparing the 2 sequences.

- Baseline HAQ-DI assumptions.

The resulting ICER was £19,114 per QALY gained. The company also used a lower baseline HAQ-DI score of 1.05 in the model, taken from Rodgers et al., which produced a slightly lower ICER of £14,390 per QALY gained.

- HAQ-DI rebound in best supportive care.

The average QALYs per patient were lower when assuming rebound to natural history, with a decrease in incremental QALYs from 0.74 in the base case (assuming a rebound to initial gain in HAQ-DI) to 0.58 in the scenario analysis. The resulting ICER was £19,114 per QALY gained. The company also used a lower baseline HAQ-DI score of 1.05 in the model, taken from Rodgers et al., which produced a slightly lower ICER of £14,390 per QALY gained.

- Alternative utility estimation using a regression function based on apremilast trial data.

The regression coefficient for the PASI score was not significantly different from zero when fitting the regression equation to apremilast trial data, indicating that psoriasis severity does not have an effect on HRQL ($p = -0.001$; 95% CI, -0.004 to 0.001). The coefficient was included in the regression because, although is not statistically significant, it was thought to be meaningful in the estimation of the utility scores. The utility scores for a HAQ-DI score of 3.0 were 0.00 and 0.41 using the co-efficients estimated by Rodgers et al. and the company, respectively. The introduction of apremilast resulted in an estimated gain of 0.36 QALYs per patient, with an ICER of £30,223 per QALY gained. The company also used utility values taken from previous submissions to NICE for adalimumab and for infliximab. The utility scores using the regression equation from the adalimumab submission were higher on average, and a unit increase in HAQ-DI score led to a smaller decrement in the utility scores than when using the equation by Rodgers et al. The resulting ICER when using utility values from the adalimumab submission was £16,754 per QALY gained. The equation used in the infliximab submission included quadratic terms for both

HAQ-DI and PASI standardised utility scores. The difference in incremental QALYs between the 2 sequences using the infliximab values was 0.01 per patient. The resulting ICER was £17,082 per QALY gained.

- Alternative estimation of best supportive and other healthcare costs based on Poole et al.

Only people receiving a TNF-alpha inhibitor were included (83% TNF-alpha inhibitor naive) in the Poole et al. study. The total annual costs included prescription costs which account for 38% of total costs. For active treatment prescription costs were excluded. Best supportive care was more expensive than in the base case but other healthcare costs were less expensive. The resulting ICER was lower than the base case at £7893 per QALY gained.

- Trial period duration of 24 weeks for apremilast.

In the scenario analyses a trial period of 24 weeks rather than 12 weeks was introduced for apremilast. Costs for the apremilast treatment sequence increased by £623 per patient with QALYs only slightly increasing (0.02) over a 40-year time horizon compared with the base case. The resulting ICER increased to £15,047 per QALY gained.

- No excess mortality is associated with psoriatic arthritis; mortality was based on general population all-cause mortality. Incremental costs increased but overall ICER was reduced slightly to £14,262 per QALY gained.

- Alternative withdrawal rates for apremilast.

In the original base case, before the company's correction at clarification stage, the withdrawal rate was considered to be 22.1%, resulting in an ICER of £14,831 per QALY gained. The company realised at the clarification stage that there was a typographical error in the withdrawal rate and that it should be

15.8% (27 out of 171), resulting in an ICER of £14,679 per QALY gained. The company applied the apremilast withdrawal rate of 15.8% across all the active treatments.

- Alternative correlation coefficient between PsARC and PASI response derived from apremilast trials.
This resulted in a slight increase in the ICER to £14,929 per QALY gained.

ERG's critique and exploratory analyses

ERG's critique of company's clinical effectiveness

- 3.28 The ERG considered that all 3 randomised placebo-controlled trials (PSA-002, -003 and -004) were of a very similar design and all were well conducted, but noted that the longer term phases of the trials, after 24 weeks, had limited clinical value. The ERG requested clarification from the company on the imputation methods used and the proportion of people with data missing. The company stated that non-responder imputation and last observation carried forward were used for the primary outcome of ACR20 and that very similar results were seen. The ERG considered this an appropriate method.
- 3.29 The ERG noted that psoriatic arthritis is normally identified through radiographic evidence of joint damage, which is also used to monitor disease progression. The company clarified that no radiographic assessments were done in the apremilast trials. The ERG considered this lack of assessment to be important because the only measure of disease progression in the trials was calculated through functional capacity using the HAQ-DI assessment (taking a mean score of the 8 categories included in the questionnaire).

- 3.30 The ERG noted that the pooled trial results presented by the company were calculated by adding together the individual trial data rather than using meta-analysis methods to calculate a pooled weighted average of the trials. The ERG stated that although this approach is generally not recommended, all 3 trials were very similar in terms of patient characteristics and study methods, therefore the results are likely to be reliable.
- 3.31 The ERG considered the pooled efficacy results at week 16 and noted that ACR50 response is a more clinically important outcome than ACR20 (see section 3.5). The proportion of people having apremilast who experienced an ACR50 response was quite low and there was uncertainty about whether the improvement in function provided by apremilast reached clinically-relevant levels. The ERG also noted that outcomes such as PsARC, MCID and HAQ-DI are prone to high response rates in the placebo group, therefore these outcomes may not provide the most informative estimates of relative efficacy.
- 3.32 The ERG stated that HAQ-DI is an important outcome in terms of a person's physical functioning and in assessing disease progression. It noted that the European Medicines Agency's assessment report commented on the HAQ-DI results for apremilast, noting that the minimum clinically important difference (MCID) for HAQ-DI in psoriatic arthritis has not been clearly established. The European Medicines Agency stated that improvements in the HAQ-DI score observed in the pooled apremilast 30 mg treatment groups exceeded the estimated MCID of -0.13 provided by 1 study (Kwok 2010), but not the estimated MCIDs of -0.3 and -0.35 provided in 2 other studies (Mease 2004 and Mease 2011). When observing the HAQ-DI data for the whole population, the ERG noted that the HAQ-DI results in the updated

network meta-analysis results did not appear plausible. The ERG asked for revised results but they were not provided before the ERG report deadline. The ERG also noted that the company had not used the updated data in the model. The ERG tried to identify the magnitude of the differences between the model inputs and the updated network meta-analysis and commented that the differences were small, were moving in the same direction and the order of treatments remained the same, and therefore the impact should not be significant.

- 3.33 During clarification the ERG requested updated sensitivity analyses using data only from people who had not had TNF-alpha inhibitor treatment for the ACR, PASI, PsARC and HAQ-DI outcomes. The company's updated analyses showed that the results were very similar to those for the overall population, because a large majority of the overall population had not had TNF-alpha inhibitor treatment. The ERG also requested a sensitivity analysis for these outcomes in people who had only had DMARD treatment rather than the total population of people who had not had TNF-alpha inhibitor treatment, because it stated that this is more likely to reflect the people who might receive apremilast in clinical practice.
- 3.34 The ERG noted that the company considered that apremilast, compared with TNF-alpha inhibitors, was likely to be associated with fewer serious adverse events over time such as serious infections and malignancies. However, the ERG could not find any clear evidence to show that apremilast had a more favourable safety profile. It also considered this argument to be inconsequential given that the company proposed apremilast in addition to a TNF-alpha inhibitor, as part of a sequence of treatments, and higher adverse events for TNF-alpha inhibitors would not be reduced by adding a therapy to the sequence.

ERG's critique of company's cost effectiveness

- 3.35 The ERG noted that the decision problem addressed by the company compared treatment sequences, including and excluding apremilast, rather than an evaluation of apremilast compared with a single comparator. It noted that the positioning of apremilast in the treatment pathway, by the company, was based on clinical expert opinion. The ERG stated that no justification was provided for why the company had positioned adalimumab before etanercept. The ERG considered that the company's approach to the decision problem represented a limited set of potentially relevant sequences.
- 3.36 The ERG noted that although the company carried out a systematic review of cost-effectiveness evidence that identified studies of biologic therapies for psoriatic arthritis, it stated that these were not directly relevant to the decision problem. The ERG considered that these studies may have provided a basis for the development of the economic model for apremilast; informing the model inputs and assumptions, and assisting in its validation.
- 3.37 The ERG stated that model submitted by the company was inflexible and only allowed the ERG to examine the use of apremilast as a pre-TNF-alpha inhibitor additional line of therapy. During clarification the ERG asked the company to provide a revised version of the model:
- allowing apremilast to replace an existing TNF-alpha inhibitor in the sequence
 - allowing apremilast to be positioned in any of the five possible lines of sequence

- including certolizumab pegol and ustekinumab as a treatment options and allowing them to be positioned in any of the possible lines of treatment
 - allowing comparison of at least 3 mutually exclusive strategies, simultaneously. Each of the strategies should allow apremilast to be included in any of the five possible lines of sequence.
- 3.38 In response the company provided an updated network meta-analysis to include ustekinumab but the ERG stated that the reporting format did not allow it to include ustekinumab as a treatment option in the economic model. The company stated that although ustekinumab was included in the final scope, it would not form part of routine established clinical practice in the management of psoriatic arthritis in England at the time of this appraisal. Similarly, the company stated that certolizumab pegol would not form part of routine established clinical practice in the management of psoriatic arthritis in England at the time of this appraisal. The company did not provide a revised economic model that allowed comparison of at least 3 mutually exclusive strategies simultaneously, because it considered that the base case incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptability curve (CEAC) provide sufficient information to adequately address the decision problem and inform the decision making process.
- 3.39 The ERG was unable to fully validate the re-submitted model because of its increased reliance on Visual Basic for Applications (VBA) language compared to the originally submitted model, with the ERG stating that the re-submitted model offered significantly less flexibility.
- 3.40 The ERG had concerns regarding a number of other approaches, assumptions and data used in the company's submission and

economic model. The ERG noted that the baseline patient characteristics in the model were taken from the pooled data from PSA-002, PSA-003 AND PSA-004, but it would have been more appropriate to use those from the studies included in the network meta-analysis because these were used to generate the treatment efficacy parameters.

- 3.41 The ERG's main concern was the key model assumption that apremilast halts HAQ-DI progression for PsARC responders while people remain on treatment, because there is no long-term clinical evidence on radiographic disease progression to support this. The ERG was also concerned about the reduction in efficacy for subsequent lines of TNF-alpha inhibitors after previous TNF-alpha inhibitors or apremilast, the monitoring costs of apremilast and disease related costs applied for HAQ and PASI, the placebo response, the application of the same withdrawal data for TNF-alpha inhibitors and apremilast, and the utility algorithm used. In addition, the ERG identified a number of data inconsistencies between the company submission and the economic model. The ERG also noted that the updated network meta-analyses, which excluded phase II trial data and unlicensed arms of apremilast, were not included in the re-submitted model.
- 3.42 The ERG was concerned about the price of infliximab used by the company in its base case analysis because the average weight of a patient was presumed to be 85.65 kg, in line with the apremilast trials. The ERG stated that the company should have used the average weight of a person as reported in the Rodgers et al. study (70 kg) because the company had utilised many of the other assumptions from this study. This would have reduced the number of vials needed for each patient. The ERG also noted that the company assumed that people would have 2 visits per year to a

- rheumatologist for any of the TNF-alpha inhibitor treatments, but only 1 visit for apremilast. The clinical expert advisers to the ERG stated that because apremilast is a new treatment more regular check-ups and monitoring are likely.
- 3.43 The ERG had concerns about the use of different trial periods for apremilast (16 weeks) and the TNF-alpha inhibitors (12 weeks) and the effect of this on clinical efficacy and the subsequent cost-effectiveness results. The ERG commented that it is not possible to know if the number of non-responders to TNF-alpha inhibitor treatment would stay the same, if the response period was extended from 12 to 16 weeks. An additional 4 weeks of treatment would be likely to increase the number of people who respond, producing a greater PsARC response rate.
- 3.44 The ERG was concerned that although the placebo PsARC response and HAQ-DI score were reported in the company's network meta-analysis, these results were not incorporated in the model or base case analyses. The ERG was also concerned about the trajectory of HAQ-DI over time, which assumed that people whose disease responded to treatment had no (zero) progression in HAQ-DI. The ERG was unsure what evidence this assumption was based on.
- 3.45 The ERG also did not agree with the company's assumption that patients did not progress (experienced full disease modification) while on apremilast. The disease modifying elements of the TNF-alpha inhibitors have been demonstrated previously using radiographic evidence, but this evidence was not available for apremilast.
- 3.46 Full details of all the evidence are in the [Committee papers](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of apremilast, having considered evidence on the nature of psoriatic arthritis and the value placed on the benefits of apremilast 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 considered the current treatment pathway for people with psoriatic arthritis. It noted that the marketing authorisation for apremilast is for 'the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy'. It heard from clinical experts that after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, most people with non-responsive disease will be treated with a tumour necrosis factor alpha inhibitor (TNF-alpha inhibitor) starting with the lowest-cost drug as recommended in NICE technology appraisal guidance on [etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis](#) and [golimumab for the treatment of psoriatic arthritis](#). The Committee also noted that NICE technology appraisal guidance on [ustekinumab for treating active psoriatic arthritis](#) is currently undergoing a rapid review, and the draft guidance recommends ustekinumab as a treatment option only if treatment with TNF-alpha inhibitors is contraindicated but would otherwise be considered, or if the person has had treatment with 1 or more TNF-alpha inhibitors. The Committee noted that the final guidance for ustekinumab was due to be published in June 2015, during the course of this appraisal. The Committee heard from the clinical

experts that use of more than 1 TNF-alpha inhibitor is established practice in the NHS; if the condition fails to respond or loses response to the first TNF-alpha inhibitor, or it causes adverse effects, a second TNF-alpha inhibitor will often be used. The patient expert emphasised that when treatment with a TNF-alpha inhibitor is contraindicated or it is stopped because of loss of effectiveness or adverse effects, there may be no alternative treatments available. The Committee concluded that treatment with a DMARD such as methotrexate, followed by TNF-alpha inhibitors in those eligible, is established practice in the NHS.

- 4.2 The Committee heard from 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 impact on people's quality of life. It can develop at a young age, and affects all aspects of a person's life including education, work, self-care, and social and family life. The Committee heard from the patient expert that skin symptoms can have a major psychological impact, and that joint symptoms can have an even greater impact on the psychological and functional aspects of living with the condition. The Committee heard from the clinical experts that the psoriatic arthritis population is heterogeneous and some people cannot tolerate DMARD therapy, or their disease does not respond adequately to it. There may, therefore, be a place in the treatment pathway for another therapy with a different mechanism of action, particularly an oral formulation, before anti-TNF inhibitors are warranted. The clinical experts noted that ustekinumab targets the interleukin-12 and -24 pathways (and that the NICE guidance is being reviewed) and that apremilast has a different mechanism of action, targeting the phosphodiesterase-4 pathway. The Committee heard from the clinical and patient experts that there is a clinical need for alternative treatments for people with both uncontrolled

psoriasis and psoriatic arthritis who cannot tolerate DMARDs, but who do not meet the diagnostic criteria to have a TNF-alpha inhibitor. The Committee concluded that patients and clinicians consider apremilast to be a valuable treatment option that could offer benefits to patients who cannot tolerate DMARDs, but who are not yet eligible for a TNF-alpha inhibitor.

- 4.3 The Committee heard from the clinical and patient experts that although methotrexate works well, some people fear the adverse effects associated with it (such as hair loss, nausea and lethargy) and the need for frequent blood tests. The experts noted that apremilast may be better tolerated, although it is associated with a higher incidence of diarrhoea initially compared with some DMARDs such as leflunomide. The clinical experts noted that there is no evidence on whether apremilast is better tolerated than TNF-alpha inhibitors and that, in general, the TNF-alpha inhibitors are well tolerated, apremilast is no better or worse than the TNF-alpha inhibitors, and the majority of patients do not experience unacceptable problems. The clinical experts also suggested that, as with any new treatment, apremilast would require extra monitoring because its long-term adverse events are unknown. The Committee concluded that apremilast has an acceptable adverse event profile in people with active psoriatic arthritis.

Clinical effectiveness

- 4.4 The Committee considered the evidence presented by the company on the clinical effectiveness of apremilast. It noted that the main sources of evidence were the PSA-002, PSA-003 and PSA-004 trials that compared apremilast (20 mg and 30 mg) with placebo in patients with active psoriatic arthritis (3 or more swollen and tender joints for at least 6 months) that had not responded to treatment with no more than 3 DMARDs or 1 TNF-alpha inhibitor. In

PSA-004 patients also had at least 1 psoriatic skin lesion of greater than 2cm. The Committee noted that the trials were well conducted and showed that apremilast is more effective than placebo after 16 weeks of treatment for a number of joint, skin and soft tissue outcomes; the primary outcome was ACR20, with a response experienced by 37% of people having apremilast compared with 19% having placebo ($p\leq 0.0001$). The clinical experts noted that apremilast was associated with a similar ACR20 response to methotrexate. The Committee also noted that apremilast was effective for associated conditions such as dactylitis and enthesitis (see section 3.6). The Committee agreed that apremilast was a clinically effective treatment compared with placebo.

- 4.5 The Committee considered the more stringent ACR outcomes (ACR50 and ACR70) presented in the apremilast trials. It heard from the clinical experts that although ACR20 is an accepted outcome measure for treatments of psoriatic arthritis and was the primary outcome in the apremilast trials, people may still have painful and swollen joints and that people start to notice a benefit at ACR50 or ACR70. The Committee agreed that there was a difference between apremilast and placebo but that the absolute differences were much less than those seen for ACR20.
- 4.6 The Committee considered the evidence from the company's network meta-analysis that compared apremilast with TNF-alpha inhibitors in the total population, and in the population who had not been treated with TNF-alpha inhibitors (see section 3.6). The Committee heard from the ERG that the methods used to identify both published and unpublished studies for the network meta-analysis were appropriate, and the studies were mostly well reported. The Committee discussed the ERG's concerns that statistical heterogeneity was tested only within-treatment and not

across the whole network, that the placebo responses (see section 4.15) for some outcomes were high which made it difficult to compare the relative efficacies of apremilast with the different comparators, and that the updated network meta-analysis results were not implemented in the model. The Committee noted that the results showed that apremilast had a clinical benefit compared with placebo. However, apremilast demonstrated a worse clinical benefit than any of the TNF-alpha inhibitors, in either population (the apremilast results were provided as academic in confidence and therefore cannot be reported). The Committee concluded that apremilast is not as clinically effective as the TNF-alpha inhibitors for treating psoriatic arthritis.

- 4.7 The Committee considered the evidence for apremilast's continued efficacy after treatment has stopped, and its ability to slow progression. It discussed the HAQ-DI outcome used by the company to calculate functional capacity and to assess disease progression. It heard from the ERG that there were uncertainties about the results because the apremilast trials were not blinded after 24 weeks and there were no stopping rules. The Committee heard that the uncontrolled part of the trial was likely to have influenced and exaggerated the HAQ-DI results. The Committee further considered the lack of radiographic assessment in the apremilast trials. It heard from the clinical experts that it would be difficult to justify using apremilast early in the treatment pathway (before TNF-alpha inhibitors) without evidence that it can prevent radiological progression, because there is evidence to show that TNF-alpha inhibitors slow disease progression. The Committee also heard from the patient experts that they want treatments that can stop the disease from progressing. The Committee accepted the views of the clinical experts that radiographic evidence, demonstrating that apremilast halts disease progression, would be

required to justify the use of apremilast before TNF-alpha inhibitors in clinical practice.

Cost effectiveness

- 4.8 The Committee discussed the assumptions in the company's model, which compared apremilast with treatment sequences rather than with a single comparator. The Committee noted that by inserting apremilast into a treatment sequence, the time spent having TNF-alpha inhibitors or best supportive care was reduced. The Committee understood that the reduction in the duration of TNF-alpha inhibitor treatment and best supportive care reduced the QALYs gained from the other treatments in the sequence. It understood that this effect would occur with the addition of any active treatment in a sequence because it prevents people transitioning to best supportive care for as long as possible (that is, the gain was not specific to apremilast treatment). Furthermore, although there was a cost associated with the insertion of apremilast into the treatment sequence, the costs of the other treatments in the sequence reduced because the time people would have subsequent TNF-alpha inhibitor treatment or best supportive care was reduced. The Committee concluded that the analyses in which treatments were substituted were more robust than those in the company's base case analysis, in which the treatment sequence was extended by the addition of apremilast.
- 4.9 The Committee considered the cost-effectiveness analyses presented in the company's submission and the critique, corrections and exploratory analyses done by the ERG. It noted the company's base-case analysis in which a post-DMARD sequence comprising of apremilast followed by 2 TNF-alpha inhibitors was compared with a sequence without apremilast. This resulted in an incremental cost-effectiveness ratio (ICER) of £14,683 (incremental

costs £10,902, incremental QALYs 0.74). The Committee noted that this was based on a level of clinical effectiveness that the clinical experts likened to that of methotrexate. However, the price of apremilast is much higher than methotrexate and closer to that of the TNF-alpha inhibitors. The Committee discussed the key assumptions used in the company's base case economic model, including: apremilast extending a treatment sequence rather than displacing a treatment, no HAQ progression after apremilast treatment, no inclusion of placebo responses, the linearity of the HAQ progression for people receiving best supportive care, the omission of relevant comparators in the NICE scope (infliximab, golimumab and ustekinumab), whether the EQ-5D data from the trial should have been implemented in the model, the different trial periods for apremilast compared with the comparators, and downgrading the effect of subsequent treatment for TNF-alpha inhibitors but not for apremilast. The Committee considered the impact of these assumptions on the cost-effectiveness estimates for apremilast.

- 4.10 The Committee considered potential comparators listed in the NICE scope such as ustekinumab and certolizumab pegol and whether they were appropriate or not. The Committee heard from the clinical experts that ustekinumab is a different class of drug to apremilast, involving a different treatment pathway, and that there is an unmet need for such treatments because approximately 10% of patients per year stop TNF-alpha inhibitor treatment. The clinical experts explained that although ustekinumab is not commonly used in clinical practice, this may change if NICE guidance recommends ustekinumab when a TNF-alpha inhibitor is contraindicated or the patient has had 1 or more TNF-alpha inhibitors. The Committee also heard that certolizumab pegol is not used in clinical practice so was not a suitable comparator. The Committee considered that

ustekinumab is an appropriate comparator for apremilast in this patient subgroup but recognised that, because ustekinumab is a recent innovation and final guidance was not yet published, it could proceed with decision making without including ustekinumab. The Committee concluded that the relevant comparators were adalimumab, etanercept, golimumab, infliximab and ustekinumab.

- 4.11 The Committee considered the company's assumptions about the improvement and progression of joint symptoms (captured using the Health Assessment Questionnaire Disability Index, HAQ-DI). It noted that these were key drivers of the economic model and that people who continued to respond to treatment at the end of the trial period retained the same HAQ-DI score (that is, apremilast was assumed to halt HAQ-DI progression while people remained on treatment and zero HAQ progression was applied). Furthermore, people who progressed to best supportive care were assumed to experience subsequent natural progression of their disease, resulting in an increase (worsening) in HAQ-DI score over time of 0.006 every 28 days, up to a maximum score of 3. The Committee noted that this score appeared high but heard from the clinical experts that although it is not possible to know if people would experience a linear progression of disease, the clinical experts considered that the increase in HAQ-DI over time is likely to be within the same range as that used by the company. The Committee heard from the ERG that experience with rheumatoid arthritis shows that HAQ-DI does not have a linear trajectory; the rate of progression of the disease slows down over time. The Committee also noted that patients with the best HAQ-DI responses would be likely to remain in the trials, making the HAQ-DI appear to improve over time. The Committee acknowledged that there is a lack of evidence to inform these model assumptions. It

concluded that the HAQ-DI input into the model represents a very optimistic modelling assumption.

- 4.12 The Committee considered the use of HAQ-DI and PASI scores mapped to EQ-5D to produce utility values of health in the company's base-case (see section **Error! Reference source not found.**). It also noted that health-related quality of life evidence had been captured directly in the apremilast trials using the EQ-5D, but the company did not use these estimates because equivalent data were not available for the TNF-alpha inhibitors. The Committee concluded that the health-related quality of life evidence from the clinical trials should have been used in the model.
- 4.13 The Committee discussed the costs included in the model, particularly the monitoring costs for apremilast treatment. It noted that the company had not included any monitoring costs for apremilast because it stated there were no specific requirements for screening or regular monitoring. The Committee heard from the clinical experts that as with any new drug, apremilast would require extra monitoring compared with current standard of care. It therefore concluded that monitoring costs for apremilast, equal to those of the TNF-alpha inhibitors, should have been included in the model.
- 4.14 The Committee considered the assumption of different trial periods for apremilast (16 weeks) and TNF-alpha inhibitors (12 weeks) for PsARC responses. The Committee heard from the ERG that the use of different time points could favour apremilast and that, if the trial period for TNF-alpha inhibitors were also increased to 16 weeks, the PsARC responses may increase. The clinical experts agreed that using different trial periods could influence the results. The Committee acknowledged that the company had carried out a scenario analysis altering the length of the apremilast

- trial period to 24 weeks but leaving the TNF-alpha inhibitor response at 12 weeks. The Committee concluded that differing trial periods could have given a relatively optimistic case for apremilast.
- 4.15 The Committee considered the company's scenario analysis in which the placebo response rate was discounted from best supportive care, but noted that it had not been discounted from the absolute response rates of apremilast or the TNF-alpha inhibitors used in the model. The Committee agreed that inclusion of placebo response rates in the model was necessary.
- 4.16 The Committee considered that the company's base case results were based on uncertain assumptions (as described in sections 4.8, 4.8, 4.11 and 4.14) and it was aware that the ERG had addressed these uncertainties in its exploratory analyses. The Committee discussed the ERG's exploratory analyses and the sequences used. The Committee heard from the ERG that due to the constraints of the company's model there were still several key areas of uncertainty that it was unable to resolve and therefore it could not present a preferred analysis. These uncertainties included the limited positions in which apremilast could be inserted into the treatment sequence, lack of flexibility to use different disease progression assumptions, the inability to add alternative comparators that had not been included in the model, and the inability within the model to apply the utility algorithm based on the apremilast data to the apremilast group. The Committee discussed all the ERG's exploratory analyses and considered that the limitations of the company's model prevented precise cost-effectiveness calculations. Nevertheless, taking the company's model together with the clinical evidence and the ERG's exploratory analysis, it explored the likely cost-effectiveness of apremilast.

- 4.17 The Committee discussed the available cost-effectiveness results for apremilast. It agreed that the ERG's exploratory analysis was a useful starting point (apremilast followed by best supportive care, compared with etanercept followed by best supportive care, and adalimumab followed by best supportive care). Even though this comparison advantaged apremilast by not dealing with the concerns set out above, apremilast was less cost-effective than etanercept or adalimumab and produced fewer QALYs compared with the TNF-alpha inhibitors (etanercept compared with apremilast resulted in an ICER of £18,997 per QALY gained, and adalimumab compared with apremilast resulted in an ICER of £23,487 per QALY gained). When apremilast was modelled to replace a first TNF-alpha inhibitor in a 2 TNF-alpha inhibitor sequence, the ICER for etanercept followed by adalimumab compared with apremilast followed by adalimumab was £33,221 per QALY gained. The Committee noted that although this calculation was affected by the limitations set out above, the ICER for the sequence without apremilast was only just above the range that is normally considered to be a cost effective use of NHS resources (up to £20,000-£30,000 per QALY gained). This was counter-intuitive given the clinical evidence (and cost) of apremilast. The Committee concluded that both the clinical evidence and the single TNF-alpha inhibitor analyses implied that apremilast, if used at all, should not be used before a TNF-alpha inhibitor.
- 4.18 The Committee discussed the ERG's exploratory analyses, in which apremilast was added to a treatment sequence. In a fully incremental analysis the most cost-effective sequence was etanercept followed by adalimumab and then by apremilast, with an ICER of £24,175 per QALY gained (incremental costs £1407, incremental QALYs 0.0582).

- 4.19 The Committee discussed what might happen to these results when the key flaws in the model were taken into account (see sections 4.8, 4.11, 4.13, 4.14 and 4.15). It considered the ERG's individual scenarios, taking into account uncertainties relating to specific parameters. Removing the assumption of reduced HAQ progression relative to best supportive care, in a simple comparison between apremilast and best supportive care, had the effect of changing the company's base case from an ICER of £14,683 to £66,045 per QALY gained. Adding a placebo response for best supportive care increased this ICER to £95,018 per QALY gained. Taking into account the monitoring costs for apremilast further increased this ICER. The Committee was aware that the ERG had not been able to model different HAQ progression assumptions (for example, considering the outcome if the HAQ progression for apremilast lay between that of best supportive care and the TNF-alpha inhibitors). The ERG had not been able to apply this, plus the placebo response and apremilast monitoring costs, to the ICERs calculated for different sequences (see sections 4.17 and 4.18) because of the model's inflexibility. However, the Committee recognised that the substantial effects of these corrections reinforced its previous - conclusions about the clinical effectiveness of apremilast and that it should not be used ahead of the TNF-alpha inhibitors. Furthermore, when taking into account the Committee's preferred assumptions for placebo response and apremilast monitoring, the ICERs were substantially more than £30,000 per QALY gained and therefore not within the range normally considered to be a cost effective use of NHS resources (up to £20,000-£30,000 per QALY gained). Therefore, apremilast alone or in combination with DMARDs was not recommended for treating people with active psoriatic arthritis that has not responded

adequately to DMARD therapy, or who cannot tolerate such therapy.

- 4.20 The Committee discussed whether apremilast is considered innovative. It heard from clinical and patient experts that apremilast may provide an additional treatment option for patients, due to its different mode of action and oral formulation. However, given its previous conclusion on clinical efficacy (see section 4.6) the Committee considered that apremilast was not a step change in treatment. The Committee concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations, and that there was no need to change its conclusions on that basis.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
	Apremilast alone or in combination with disease-modifying antirheumatic drug (DMARD) therapy is not recommended within its marketing authorisation; that is, for treating adults with active psoriatic arthritis that has not responded to a prior disease-modifying antirheumatic drug (DMARD) therapy, or such therapy is not tolerated..	1.1
	When taking into account the Committees' preferred assumptions for Health Assessment Questionnaire Disability Index (HAQ-DI) progression, placebo response and apremilast monitoring, the ICERs were substantially over £30,000 per QALY gained and not within the range normally considered to be a cost effective use of NHS resources (up to £20,000-£30,000 per QALY gained).	4.19

Current practice		
Clinical need of patients, including the availability of alternative treatments	<p>The Committee noted that following treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) most people with non-responsive disease will be treated with a TNF-alpha inhibitor and treatment will be started with the lowest cost drug.</p> <p>The Committee noted there is an unmet need for treatments using alternative pathways to TNF-alpha inhibitors because approximately 10% of patients per year stop TNF-alpha inhibitor treatment.</p>	4.1 4.10
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	It heard from clinical and patient experts that apremilast may provide an additional treatment option for patients, due to its different mode of action and oral formulation. However, given its previous conclusion on clinical efficacy the Committee considered that apremilast was not a step change in treatment.	4.20
What is the position of the treatment in the pathway of care for the condition?	The Committee concluded that patients and clinicians considered apremilast to be a valuable treatment option that could offer benefits to patients who cannot tolerate	4.2

	<p>DMARDs, but who are not yet eligible for a TNF-alpha inhibitor.</p> <p>The Committee considered that ustekinumab is an appropriate comparator for apremilast in this patient subgroup but recognised that, because ustekinumab is a recent innovation and final guidance was not yet published, it could proceed with decision making without including ustekinumab. The Committee concluded that the relevant comparators were adalimumab, etanercept, golimumab, infliximab and ustekinumab.</p>	4.10
Adverse reactions	<p>The Committee concluded that apremilast has an acceptable adverse event profile in people with active psoriatic arthritis.</p>	4.3
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	<p>The Committee noted that the main sources of evidence were the PSA-002, PSA-003 and PSA-004 trials that compared apremilast (20 mg and 30 mg) with placebo. It concluded that these trials were well conducted.</p> <p>The Committee considered the evidence from the company's network meta-analysis that compared apremilast with TNF-alpha inhibitors in the total population, and in the population who had not been treated with TNF-alpha inhibitors. The Committee heard from the ERG that the methods used to</p>	4.4 4.6

	identify both published and unpublished studies for the network meta-analysis were appropriate and the studies were mostly well reported. The Committee concluded that apremilast is not as clinically effective as the TNF-alpha inhibitors for treating psoriatic arthritis.	
Relevance to general clinical practice in the NHS	The Committee understood that treatment with a DMARD such as methotrexate, followed by use of TNF-alpha inhibitors in those eligible, is established practice in the NHS but that there is an unmet need for treatments that have a different mechanism of action to TNF-alpha inhibitors.	4.1, 4.10
Uncertainties generated by the evidence	<p>The Committee discussed the ERG's concerns that statistical heterogeneity was tested only within-treatment and not across the whole network meta-analysis, that the placebo responses for some outcomes were high which made it difficult to compare the relative efficacies of apremilast with the different comparators, and that the updated network meta-analysis results were not implemented in the model.</p> <p>The Committee heard from the ERG that there were uncertainties about the PSA-002, -003 and -004 trial results because the trials were not blinded after 24 weeks and there were no stopping rules. The Committee heard that the</p>	4.6 4.7

	uncontrolled part of the trial was likely to have influenced the HAQ-DI results. The Committee further considered the lack of radiographic assessment in the apremilast trials.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No specific Committee consideration.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee heard that apremilast was associated with a similar ACR20 response to methotrexate. It noted that apremilast appeared to be effective across a range of skin and joint outcomes and that it was effective for associated conditions such as dactylitis and enthesitis. The Committee agreed that apremilast was a clinically effective treatment compared with placebo.	4.4
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee noted that the company's model compared apremilast with treatment sequences rather than with a single comparator. The Committee noted that health-related quality of life evidence had been captured directly in the apremilast trials using the EQ-	4.8 4.12

	5D, but the company did not use these in its submission. The Committee concluded that the health-related quality of life evidence from the clinical trials should have been used in the model.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that by inserting apremilast into the sequence, the time spent receiving TNF-alpha inhibitors or best supportive care and the QALY gains were reduced. It heard from the ERG this effect would occur with the addition of any active treatment in a sequence because it prevents the transition to best supportive care for as long as possible (that is, the gain was not specific to apremilast treatment).	4.8
Incorporation of health-related quality-of-life benefits and utility values	The Committee considered the company's assumptions about the improvement and progression of joint symptoms (captured using the Health Assessment Questionnaire Disability Index, HAQ-DI). It heard that people who progressed to best supportive care were assumed to experience subsequent natural progression of their disease, resulting in an increase (worsening) in HAQ-DI score of 0.006 per 28 days over time, up to a maximum score of 3. The Committee noted that this score appeared high but heard from the clinical experts that they would expect a HAQ-DI score in this region. The Committee heard from the ERG that experience with	4.11

	<p>rheumatoid arthritis shows that HAQ-DI does not have a linear trajectory. It concluded that the HAQ-DI input into the model represents a very optimistic modelling assumption.</p> <p>The Committee did not hear that there were any additional gains in health-related quality of life over those already included in the QALY calculations.</p>	4.20
Are there specific groups of people for whom the technology is particularly cost effective?	No specific Committee consideration.	-
What are the key drivers of cost effectiveness?	<p>The Committee noted that by inserting apremilast into a treatment sequence rather than displacing a treatment, the time spent receiving TNF-alpha inhibitors or best supportive care, and the QALYs gained, was reduced.</p> <p>The Committee noted that the HAQ-DI was a key driver of the economic model and that people who continued to respond to treatment</p>	4.8 4.11

	<p>at the end of the trial period retained the same HAQ-DI score. The Committee also noted that patients with the best HAQ-DI responses would be likely to remain in the trials, making the HAQ-DI appear to improve over time.</p> <p>The Committee noted that the company had not included any monitoring costs for apremilast, even though it would require extra monitoring compared with current standard of care.</p> <p>The Committee considered the assumption of different trial periods for apremilast (16 weeks) and the TNF-alpha inhibitors (12 weeks) for PsARC responses and heard that the use of different time points could favour apremilast.</p> <p>The Committee also considered the inclusion of placebo response rates in the model, and concluded that this was necessary.</p> <p>The Committee was also aware of a number of uncertainties highlighted by the ERG including; the limited positions in which apremilast could be inserted into the treatment sequence, lack of flexibility to use different disease progression assumptions, the inability to add alternative comparators that had not been included in the model and the inability within the model to apply the utility algorithm based on the apremilast data to the apremilast</p>	4.13
		4.14
		4.15
		4.16

	group.	
Most likely cost-effectiveness estimate (given as an ICER)	When taking into account the Committee's preferred assumptions for HAQ, placebo response and apremilast monitoring, the ICERs were substantially over £30,000 per QALY gained and therefore not within the range normally considered to be a cost effective use of NHS resources (up to £20,000-£30,000).	4.19
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	-
End-of-life considerations	Not applicable	-
Equalities considerations and social value judgements	Not applicable	-

5 Implementation

5.1 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Ustekinumab for treating active psoriatic arthritis \(rapid review of technology appraisal guidance 313\)](#). NICE technology appraisal guidance 340 (2015).
- [Ustekinumab for treating active and progressive psoriatic arthritis](#). NICE technology appraisal guidance 313 (2014).
- [Golimumab for the treatment of psoriatic arthritis](#). NICE technology appraisal guidance 220 (2011).
- [Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis](#) (superseded technology appraisals No. 104 & 125). NICE technology appraisal guidance 199 (2010).

7 Proposed date for review of guidance

- 7.1 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.

Professor Andrew Stevens
Chair, Appraisal Committee
June 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE.

Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

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

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel

Institute of Brain and Behaviour Mental Health, University of Manchester

Dr David Black

Medical Director, NHS South Yorkshire and Bassetlaw

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health,
University College London

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics, and Acute Physician,
Leicester Royal Infirmary

Dr Patrick McKiernan

Consultant Paediatrician, Birmingham Children's Hospital

Dr Suzanne Martin

Reader in Health Sciences

Dr Paul Miller

Market Access Advisor

Dr John Radford

GP, NHS Sheffield

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS
Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of
Sheffield

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle

Lay Member

NICE project team

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

Dr Caroline Hall

Technical Lead

Fay McCracken

Technical Adviser

Lori Farrar

Project Manager

9 Sources of evidence considered by the Committee

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

- Corbett M, Sideris E, Palmer S, et al., Apremilast for treating active psoriatic arthritis: A single technology appraisal, March 2015

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

I. Company:

- Celgene

II. Professional/expert and patient/carer groups:

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

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Abbvie (adalimumab)

- Merck Sharp & Dohme (golimumab, infliximab)
- Hospira UK (infliximab biosimilar [Inflectra])
- Napp Pharmaceuticals (infliximab biosimilar [Remsima])
- Centre for Reviews and Dissemination and Centre for Health Economics – York
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Ciclosporin for treating dry eye disease by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Phillip Helliwell, Senior Lecturer in Rheumatology, nominated by British Society of Rheumatology and Arthritis Research UK – clinical expert
- Dr Ruth Murphy, Consultant Dermatologist, nominated by British Association of Dermatologists and Royal College of Physicians – clinical expert
- David Chandler, Chief Executive, nominated by Psoriasis and Psoriatic Arthritis Alliance – patient expert
- Helen McAteer, Chief Executive, nominated by Psoriasis Association – patient expert

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

- Celgene