Apremilast for treating active psoriatic arthritis

Technology appraisal guidance
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# Contents

1 Guidance .......................................................................................................................... 3

2 The technology .................................................................................................................. 4

3 The company's submission ............................................................................................... 5
   Clinical effectiveness ........................................................................................................ 5
   Cost effectiveness ............................................................................................................ 8
   ERG's critique and exploratory analyses ......................................................................... 10

4 Consideration of the evidence ......................................................................................... 22
   Clinical need and practice ............................................................................................. 22
   Clinical effectiveness ..................................................................................................... 24
   Cost effectiveness .......................................................................................................... 26
   Summary of Appraisal Committee's key conclusions .................................................... 33

5 Review of guidance .......................................................................................................... 43

6 Appraisal Committee members, guideline representatives and NICE project team ........ 44
   Appraisal Committee members ................................................................................... 44
   NICE project team ....................................................................................................... 46

7 Sources of evidence considered by the Committee .......................................................... 47

8 About this guidance........................................................................................................... 49
1 Guidance

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 6) considered evidence submitted by Celgene and a review of this submission by the Evidence Review Group (ERG; section 7).

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 (PSA-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: Maastricht Ankylosing Spondylitis Enthesitis Score (MASES); dactylitis severity scores; ACR50; and ACR70. Data were collected at weeks 16, 24 and 52. 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. An ACR20 response was experienced by 37% of people having apremilast compared with 19% having placebo (p≤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≤0.0001), PsARC response (49% and 30% respectively; p≤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≤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 for the outcomes PsARC, ACR 20/50/70, PASI, and HAQ-DI. 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 NICE and 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 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 people who have not had TNF-alpha inhibitor treatment. The apremilast results were provided as academic in confidence and therefore cannot be reported.

3.9 The highest probabilities of PsARC response for the whole population were seen with golimumab 50 mg followed by golimumab 100 mg and infliximab 5 mg/kg. Probability of PsARC response with apremilast was lower than all of the other active treatments. 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 for the whole population 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.

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.

3.13  Adverse events were not a primary outcome in any of the trials, however, the trials did record serious adverse events, severe adverse events and adverse events leading to discontinuation from treatment. The company 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

Company's original submission

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 a half-cycle correction to the model because it considered the cycle to be sufficiently short. 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. 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 (that is, people whose disease did not show a response to treatment in the 16-week trial period). This was because of a likely reduction in the efficacy of TNF-alpha inhibitors if used again 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 (Rodgers et al. 2011) based on data from the ADEPT trial (correlation coefficient 0.436). 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 provided results for their original base case. However, in response to uncertainties raised about the model in the appraisal consultation document, the company submitted a revised base case. The Committee accepted these revisions and therefore all original analyses have now been superseded.

**ERG's critique and exploratory analyses**

**ERG comments on the company's original submission**

3.20 The ERG considered that all 3 randomised placebo-controlled trials (PSA-002, PSA-003 and PSA-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 because of factors including a lack of control groups, lack of adequate blinding (particularly important because many outcomes were patient-reported), and lack criteria for stopping treatment. NICE and 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.

3.21 The ERG noted that radiographic evidence of joint damage can be 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).

3.22 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.

3.23 The ERG considered the pooled efficacy results at week 16 and noted that ACR50 response is a more clinically important outcome than ACR20. 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.

3.24 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, moving in the same direction and the order of treatments remained the same, and therefore the impact should not be significant.
During clarification NICE and 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 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 in the original submission**

The ERG noted that the decision problem addressed by the company compared treatment sequences, including and excluding apremilast, and did not provide a cost-effectiveness analysis 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 considered that the company’s approach to the decision problem represented a limited set of potentially relevant sequences and possible positions of apremilast in the treatment sequence.

The ERG noted that the company carried out a systematic review of cost-effectiveness evidence that identified studies of biological therapies for psoriatic arthritis, and stated that these were not directly relevant to the decision problem. However, the ERG considered that the studies could have provided a basis for the development of the economic model for apremilast; informing the model inputs and assumptions, and assisting in its validation.

The ERG stated that the original company model was not flexible and only allowed the ERG to examine the use of apremilast as an additional line of therapy before TNF-alpha inhibitors. During clarification NICE and 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 5 possible lines of sequence

• including certolizumab pegol and ustekinumab as 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 5 possible lines of sequence.

3.30 In response the company provided an updated network meta-analysis to include ustekinumab and the ERG stated that the format of the economic model did not allow it to include ustekinumab as a treatment option. The company further stated that although ustekinumab was included in the final scope (as a possible comparator subject to a NICE technology appraisal of ustekinumab), 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, and for this reason it had not included these comparisons in its analyses. Finally, 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.

3.31 The ERG was unable to fully validate the re-submitted model because of its increased reliance on Visual Basic for Applications (VBA) language compared with the originally submitted model.

3.32 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 characteristics from the studies included in the network meta-analysis because these were used to generate the treatment efficacy parameters.
3.33 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 company's assumptions of a 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-DI and PASI, the placebo response in the model being different from that seen in the trials, 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 network meta-analyses updated after clarification, which excluded phase II trial data and unlicensed arms of apremilast, were not included in the re-submitted model.

3.34 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.

3.35 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 for that treatment group (apremilast).

3.36 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.

3.37 The ERG 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 is not available for apremilast at this time.

New evidence submitted by the Company in response to the appraisal consultation document

3.38 The company was granted permission to provide new evidence and new cost-effectiveness analyses (see sections 3.39 to 3.44) to respond to some areas of uncertainty raised by the Committee and documented in the appraisal consultation document.

3.39 The company provided additional clinical evidence on the following:

- Radiographic progression of disease: the company stated that the association between joint damage and functional decline is not well defined, and that evidence suggests that structural joint damage is slow and sub-clinical, therefore a significant decline is needed before there is a meaningful impact on function. It also stated that a study of the comparator drug golimumab by Kavanaugh et al. (2015) showed that control of disease symptoms was associated with less radiographic progression and better functional outcomes. It further stated that apremilast has demonstrated long-term control of disease symptoms. The company stated that its interpretation of, and conclusions about, this evidence was supported by a number of leading rheumatologists.

- The long-term safety of apremilast: the company provided 3 year pooled data about adverse events for apremilast from trials PSA-002, PSA-003, and PSA-004.

- Uncertainty in HAQ-DI scores because of the unblinded period of the apremilast trials: the company explained that the design of their pivotal trials were standard, with the placebo period minimised for ethical reasons, and that patients and investigators remained blinded to initial treatment and current dosage, even in the unblinded
period. The company also provided analyses to show that the HAQ-DI score was unlikely to be subject to bias:

- The company tested different imputation strategies to derive missing values for long-term outcomes for week 16 PsARC responders. It found that the week 52 HAQ-DI score was consistent with week 16, and concluded that the outcome was robust to different imputation strategies.

- The company compared the correlation coefficients in the blinded (week 16) and unblinded (week 52) trial periods between patient reported outcomes (HAQ-DI) and objective physician-assessed outcomes (swollen/tender joint count). It found no significant differences.

3.40 The company's new cost-effectiveness analysis included the following amendments to its original base-case analysis:

- Including updated network meta-analysis results supplied as part of clarification (excluding the Schett et al. study, which included unlicensed doses of apremilast).

- A revised utility function based on apremilast trial data using UK tariff sets for EQ-5D utility values applied to all treatments (and not US tariffs, as had been incorrectly used by the company in a scenario analysis in the original base case). The company stated that a comparison of the revised utility function with the Rodgers et al. function used in its original base case indicated that the 2 functions were similar.

- Inclusion of a placebo response in the best supportive care health state, in line with the trial outcome data (see section 3.5).

- Physician visits and monitoring frequency assumed to be the same for apremilast and TNF-alpha inhibitor therapies (the Committee's preferred scenario in the appraisal consultation document). The company accepted that initially there would be higher than usual levels of monitoring (as with any active treatment), and stated that in the longer term the frequency would reduce. It further stated that the original assumption of less monitoring, used in the original model, was based on clinical opinion and the summary of product characteristics.

3.41 The company presented new base-case analyses, sensitivity analyses and scenario analyses. The revised base case was based on the same treatment sequence as in the original base case (that is, apremilast, adalimumab, etanercept and best supportive care compared with adalimumab, etanercept and best supportive care). The company noted that, in the appraisal consultation
document, the Committee had expressed a preference for scenarios in which treatments were substituted. The company emphasised its original position that the sequencing modelling approach accurately reflected how apremilast would be used in clinical practice, and that this was supported by a number of rheumatologists. However, it did present a treatment substitution scenario (see section 3.44).

3.42 The results from the company’s new cost-effectiveness analyses are presented in table 1. The revised base case ICER was £19,510 per quality-adjusted life year (QALY) gained (incremental costs £12,046, incremental QALYs 0.62).

Table Company’s revised base case and other scenarios

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Cost (£)</th>
<th>QALYs</th>
<th>Inc. costs (£)</th>
<th>Inc. QALYs</th>
<th>ICER (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1: Original base case sequences using updated NMA results</strong></td>
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<td><strong>5: Scenario 4 plus no decline in efficacy assumed for TNF-alpha inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>108,051</td>
<td>7.98</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Apremilast</td>
<td>119,379</td>
<td>8.56</td>
<td>11,328</td>
<td>0.58</td>
<td>19,699</td>
</tr>
</tbody>
</table>
Comparator arm: adalimumab, etanercept, best supportive care.
Apremilast arm: apremilast, adalimumab, etanercept, best supportive care.
Abbreviations: BSC, best supportive care; Inc., incremental; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality adjusted life year; TNF, tumour necrosis factor.

3.43 The company’s deterministic results showed the ICER was most sensitive to the slope of HAQ-DI. When assuming HAQ-DI progression of 0.001 per cycle when not on treatment (and not 0.006 as in the base case), the ICER was £54,629 per QALY gained. The company’s probabilistic results showed that the probability of cost effectiveness at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained were less than 50%, and 86%, respectively.

3.44 The company did a number of scenario analyses:

- HAQ-DI progression: the company varied the HAQ-DI progression rate for apremilast in relation to best supportive care (assuming best supportive care progression rate of 0.006 per cycle). The lowest ICER was £22,667 per QALY gained (HAQ-DI progression for 100% of apremilast patients at a rate equal to best supportive care, with dropout at HAQ-DI score of 1.18) and the highest ICER was £29,117 per QALY gained (as previous ICER, but with dropout at HAQ-DI score of 2). However, the company stated that it was unreasonable to assume that the HAQ-DI for all patients declined over time, because there is evidence that HAQ-DI response is maintained for at least 2 years, and that approximately 10% of people having apremilast who show an initial clinical response may experience some degree of worsening of HAQ-DI while having therapy (supported by week 104 trial data). The company also stated that clinical opinion suggests that patients would likely move to another treatment if HAQ-DI score worsened to 2 while having apremilast therapy.

- Apremilast given before TNF-alpha inhibitors, compared with apremilast given after TNF-alpha inhibitors: the company compared apremilast, adalimumab, etanercept and best supportive care with adalimumab, etanercept, apremilast and best supportive care, generating an ICER of £13,716 per QALY gained (that is, apremilast was more cost effective when given before TNF-alpha inhibitors).

- Increasing the length of treatment sequences by adding further TNF-alpha inhibitors: when comparing a sequence of apremilast, adalimumab, etanercept, golimumab, infliximab and best supportive care with a sequence of adalimumab, etanercept,
golimumab, infliximab and best supportive care, the ICER was £16,596 per QALY gained. The ICER was £19,946 per QALY gained when comparing a sequence of apremilast, adalimumab, etanercept, golimumab and best supportive care with a sequence of adalimumab, etanercept, golimumab and best supportive care.

- Treatment substitution: the company did a scenario in which apremilast was used instead of adalimumab in a sequence of adalimumab, etanercept, golimumab and best supportive care. The ICER generated was £1437 per QALY gained (incremental costs £239, incremental QALYs 0.17). The company considered this scenario to be of limited relevance, stating that the revised base case (apremilast as an addition to a treatment sequence) was the most accurate representation of the expected use of apremilast in clinical practice, and that this opinion was supported by rheumatologists.

- Comparison of apremilast against best supportive care only: the ICER was £25,220 per QALY gained (assuming HAQ-DI progression for apremilast is equal to rate of best supportive care, and dropout at HAQ-DI score of 3) or £21,706 (assuming that HAQ-DI progression is equal to half the rate of that for best supportive care). However, the company stated that best supportive care was not an appropriate comparator given the proposed positioning of apremilast.

**ERG’s critique of additional analyses presented by the company during consultation**

3.45 The ERG provided the following critique about the responses from the company:

- Radiographic progression: the ERG agreed that control of disease symptoms improves long-term functional and joint damage outcomes. However, it stated that apremilast is less effective than other active treatments for outcomes including HAQ-DI, PASI, and PsARC. It also stated that the comparator TNF-alpha inhibitors have radiographic evidence of effectiveness for peripheral arthritis and radiographic progression, unlike apremilast.

- Utility values: the ERG agreed that UK EQ-5D data is more appropriate than US data. It noted that when UK values are used, the utility function is very similar to the function derived using Rodgers et al. that was used in the original base case.

- HAQ-DI: the ERG stated that the long-term impact of apremilast is still unknown, and that techniques for estimating missing data are not appropriate when data cannot be assumed to be missing at random.
Monitoring: clinical advisers to the ERG stated that assuming similar monitoring for apremilast and the comparators is appropriate, because apremilast is a new medication, there is likely to be a high proportion of concomitant DMARD use, and patient adherence needs to be ensured.

Treatment sequence: the ERG stated that the company had presented a limited set of treatment sequences, which were not sufficient to inform the most efficient place for apremilast in the treatment sequence.

The ERG provided scenario analyses including apremilast compared with a single therapy, treatment sequences with and without apremilast, treatment sequences with an equal number of active comparators before best supportive care, and varying rates of HAQ-DI progression (all HAQ-DI scenarios assumed patients would stop the treatment being received at a HAQ-DI score of 2). The ERG commented that it was unable to validate how HAQ-DI progression was applied in the company’s additional analyses, for patients having apremilast. It noted that HAQ-DI progression on apremilast seemed to have been applied correctly when apremilast was the first treatment in the sequence. However, it was unable to validate whether it had been applied appropriately when apremilast was not the first treatment in the sequence. Apremilast resulted in cost savings but a QALY loss in all of the ERG’s exploratory analyses:

Direct comparisons (1 active treatment followed by best supportive care):

- Compared with etanercept, the ICER ranged from £17,779 saved per QALY lost (when assuming that HAQ-DI progression for apremilast was equal to the rate for best supportive care) to £22,561 saved per QALY lost (when assuming that apremilast had no HAQ-DI progression).

- Compared with adalimumab, the ICER ranged from £18,764 saved per QALY lost (when assuming HAQ-DI progression at a rate equal to that for best supportive care) to £29,110 saved per QALY lost (when assuming no HAQ-DI progression for apremilast).

Treatment sequences with an equal number of active comparators before best supportive care, and before TNF-alphas inhibitors (comparing a sequence of apremilast, adalimumab, etanercept and best supportive care with adalimumab, etanercept, golimumab and best supportive care). The ICERs were:
- £15,088 saved per QALY lost (assuming HAQ-DI progression at the same rate as that for best supportive care), cost savings of £6924 and a QALY loss of −0.459

- £18,288 saved per QALY lost (assuming HAQ-DI progression at half the rate of that for best supportive care), cost savings of £6739 and a QALY loss of −0.368

- £27,134 saved per QALY lost (when using the company base case assumptions), cost savings of £6930 and a QALY loss of −0.255.

- Treatment sequences with an equal number of active comparators before best supportive care, and after TNF-alpha inhibitors (using apremilast instead of golimumab in a sequence of adalimumab, etanercept, golimumab and best supportive care). The ICERs were:
  - £11,518 per QALY lost (HAQ-DI progression at the same rate of best supportive care), cost savings of £5630 and a QALY loss of −0.489
  - £14,781 per QALY lost (HAQ-DI progression at half the rate of best supportive care), cost savings of £5343 and a QALY loss of −0.362
  - £26,573 saved per QALY lost (company base case assumptions) cost savings of £5599 and a QALY loss of −0.211.

3.47 Full details of all the evidence are available.
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 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 concluded that psoriatic arthritis substantially decreases quality of life.

4.2 The Committee considered the current treatment pathway for people with psoriatic arthritis. 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 (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. It heard from the clinical experts that use of more than 1 TNF-alpha inhibitor is established practice in the NHS; if the disease 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 Committee considered where apremilast would fit into this existing treatment pathway. It heard from the patient expert that when treatment with a TNF-alpha inhibitor is contraindicated, or it is stopped because of loss of effectiveness or adverse effects (the clinical experts noted approximately 10% of patients per year stop TNF-alpha inhibitor treatment), there may be no alternative treatments available. Therefore, patients and clinicians value having a range of treatment options available, and there is an unmet need for treatments that offer a
different mechanism of action to the TNF-alpha inhibitors or that are administered orally, as with apremilast (a phosphodiesterase-4 inhibitor).

4.3 The Committee was aware that apremilast had the same marketing authorisation as the currently recommended biological treatments, but that the company had stated that apremilast would be used before these treatments in clinical practice, based on its oral route of administration, safety profile compared with current biological and conventional DMARD treatments, no specific requirements in the marketing authorisation for regular monitoring, and a cheaper cost compared with current biological therapies. The Committee was also aware of a written statement from the clinical expert that apremilast could be considered an alternative first or second line drug, because it was likely more effective than methotrexate. However, the written statement from the clinician had noted that placement in the pathway would also depend on treatment cost. The Committee heard from the clinical experts that it would be useful to have an additional treatment option before TNF-alpha inhibitors, because the psoriatic arthritis population is heterogeneous and some people cannot tolerate DMARD therapy, or their disease does not respond adequately to it. The Committee concluded that it was possible that apremilast could be used as a treatment before TNF-alpha inhibitors, but that any use or positioning of apremilast would need to be supported by clinical and cost-effectiveness evidence, particularly because several effective treatment options are already recommended for psoriatic arthritis.

4.4 The Committee considered the most appropriate comparators for this appraisal. It was aware that during the course of this appraisal (in June 2015), NICE had published guidance on ustekinumab for treating active psoriatic arthritis which, as an IL12/23 inhibitor, offered a different mechanism of action to the TNF-alpha inhibitors. However, it accepted that current usage of this drug was likely to be low, both because it had only recently received a positive recommendation, and also because the recommendation is more restrictive than the currently recommended TNF-alpha inhibitors (ustekinumab is recommended 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 was also aware that certolizumab pegol (another TNF-alpha inhibitor) is another possible treatment option for people with psoriatic arthritis; however, it heard from the clinical experts that it is rarely used in clinical practice. The Committee
concluded that the most appropriate comparators for this appraisal were the TNF-alpha inhibitors adalimumab, etanercept, infliximab and golimumab (because they have a similar marketing authorisation to apremilast, and are the most commonly used treatments in clinical practice after the failure of a DMARD) and that ustekinumab could be considered as a comparator if it became relevant to consider making a recommendation specifically for a population for whom TNF-alpha inhibitors are not appropriate.

4.5 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 stated 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 stated 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 need extra monitoring because its long-term adverse events are unknown. The Committee was aware of new evidence about the adverse effects of apremilast that the company had submitted in response to the appraisal consultation document, which provided further evidence about the adverse event profile for apremilast. The Committee concluded that apremilast has an acceptable adverse event profile in people with active psoriatic arthritis.

**Clinical effectiveness**

4.6 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 up to 3 DMARDs or 1 TNF-alpha inhibitor. 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 American College of Rheumatology response criteria (ACR20), with a response experienced by 37%
of people having apremilast compared with 19% having placebo ($p<0.0001$). The clinical experts noted that apremilast was associated with a similar ACR20 response to methotrexate. The Committee acknowledged that in response to the appraisal consultation document the company stated that it considered this opinion to be subjective, because little comparative evidence is available in this area. The Committee also noted that apremilast was effective for associated problems such as dactylitis and enthesitis (see section 3.6). The Committee agreed that apremilast was a clinically effective treatment compared with placebo.

4.7 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 less than those seen for ACR20.

4.8 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 3.8 to 3.12). The Committee heard from the Evidence Review Group (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 the placebo responses (see section 3.33) for some outcomes were high which made it difficult to compare the relative efficacies of apremilast with the different comparators. The Committee noted that the results showed that apremilast had a clinical benefit compared with placebo. However, apremilast demonstrated less 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.

4.9 The Committee considered the Health Assessment Questionnaire Disability Index (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 from the apremilast trials because they were not blinded after 24 weeks and there were no stopping rules, which was likely to have influenced the HAQ-DI results. The Committee noted that the company had provided evidence to argue against this in its response to the appraisal consultation document (see section 3.39); for example, the company stated that participants remained blinded to initial treatment and dose during the unblinded period. However, the Committee remained concerned that, in comparison with more objective measures of disease progression such as radiographic assessments, there was a higher possibility of bias.

4.10 The Committee 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. It noted that the company had stated in its response to the appraisal consultation document that the relationship between radiographic progression and functional capacity was unclear, and that other measures such as disease activity were equally, if not more, important when considering the impact of disease on quality of life. The Committee accepted that it may be necessary to interpret radiographic evidence with caution, and that disease activity outcomes play an important role in functional capacity. However, it noted that apremilast not only lacked radiographic evidence about disease progression, but had consistently shown the worst performance of any active comparator for all outcomes presented in the network meta-analyses (see section 3.8 to 3.12). Because it is a new treatment, there is a lack of long-term clinical effectiveness data for apremilast. The Committee concluded that the lack of radiographic evidence and the clinical-effectiveness evidence did not support the use of apremilast before TNF-alpha inhibitors in clinical practice.

Cost effectiveness

4.11 The Committee considered the company’s revised model which, as in the original base case, compared treatment sequences with and without apremilast, rather than comparing apremilast with a single comparator. This provided a revised base-case incremental cost-effectiveness ratio (ICER) of approximately
£19,500 per quality-adjusted life year (QALY) gained when adding apremilast to a treatment sequence of adalimumab, etanercept, and best supportive care (see table 1). Apremilast remained cost effective (when assuming a maximum acceptable ICER of £30,000 per QALY gained) in exploratory analyses, including when varying apremilast HAQ-DI progression in relation to best supportive care (£22,700 to £29,100 per QALY gained, see section 3.44). The Committee accepted that the use of treatment sequences was a valid approach to modelling.

4.12 The Committee considered whether the structural and parameter assumptions in the company’s treatment sequences in the revised base case reflected clinical practice. It noted that the majority of analyses by the company compared treatment sequences that had a different number of active comparators before progression to best supportive care, with the base case comparing 3 active treatments for the apremilast group with 2 for the comparator group. The Committee agreed that, in clinical practice, patients would likely receive more than the 2 active treatments patients were assumed to receive in the comparator group before they progressed to best supportive care. This was because there are a number of active comparators available for treating psoriatic arthritis, particularly since the positive recommendation for ustekinumab. The Committee also considered that models comparing sequences, rather than more traditional direct comparisons, created additional uncertainty in the model. Treatment sequences of different lengths may exacerbate uncertainties in the model, which may also be less easily identifiable, because they are less likely to affect each arm equally than with direct comparisons or equal length sequences. The Committee further understood from the Assessment Group analyses that, assuming all other things were equal, replacing apremilast in the intervention group of the company revised base case with any of the TNF-alpha inhibitors would result in a QALY gain over the comparator sequence. The Committee concluded that in order to prevent the model being confounded by any QALY gain occurring only because of one group in the model having an additional active treatment, in a selected and unrealistically short sequence, it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence.

4.13 The Committee noted that the company had presented a limited exploratory analysis using treatment sequences of equal length in which apremilast was used instead of adalimumab in a sequence of adalimumab, etanercept,
golimumab and best supportive care. However, the Committee noted that this needed to be seen in the context of the ERG's multiple calculations using sequences with an equal number of active comparators, and also noted that the company considered this scenario to be of limited relevance. The Committee also noted that the analyses should be consistent with the direct clinical and cost differences between the TNF-alpha inhibitors and apremilast.

4.14 The Committee considered the company's assumptions about the improvement and progression of joint symptoms (measured using HAQ-DI). It noted that these were key drivers of the economic model and that people whose disease 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, therefore zero HAQ-DI progression was applied). The Committee noted that the company's rationale for assuming that apremilast halts disease progression was based on acceptance in previous NICE appraisals for psoriatic arthritis that TNF-alpha inhibitors halt disease progression. The Committee was aware that the assumption that TNF-alpha inhibitors halt disease progression was supported radiographically and also by clinical practice evidence over a number of years. However, there was uncertainty about whether this assumption was equally relevant for apremilast, which has a different mechanism of action and limited evidence of use in clinical practice because it is a relatively new treatment. The Committee also noted 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 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. However, the Committee also noted comments from the company in response to the appraisal consultation document that the linearity of HAQ-DI progression was hypothetical and that the previous appraisal for ustekinumab for treating active psoriatic arthritis had assumed linear progression. 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, and this added uncertainty to the model. However, the assumption that apremilast completely halts HAQ-DI progression represented a best-case scenario that was not supported by clinical evidence (see sections 4.8, 4.9 and 4.10).

4.15 The Committee considered the use of HAQ-DI and Psoriasis Area Severity Index (PASI) scores mapped to EQ-5D to produce utility values of health in the company's original base case. The Committee noted that the utility values in the company's revised base case were derived from the apremilast trial. Although this reflected the preferences of the Committee as expressed in the appraisal consultation document, the Committee noted that this had little impact on results compared with the values used in the original base case. The Committee was also surprised at the estimates of utility, which appeared very low and similar to technologies for end of life conditions. However, the Committee agreed that the company had used a legitimate source for utility values by using the available trial data, and accepted the utility values for its decision-making.

4.16 The Committee discussed the costs included in the model, particularly the monitoring costs for apremilast treatment. It noted that in response to the appraisal consultation document the company had stated that monitoring costs for apremilast should not be included because there were no specific requirements for screening or regular monitoring, but that it had updated its revised base case to include an equal level of monitoring for all active treatments. The Committee heard from the clinical experts that, as with any new drug, apremilast would initially require more monitoring compared with the current standard of care. It therefore concluded that the revised model had correctly accounted for monitoring costs for apremilast.

4.17 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 the longer trial period of apremilast could have given a relatively optimistic case for apremilast compared with other comparators.

4.18 The Committee considered the company's assumptions for placebo responses in the original and revised model. It noted that in the original model, the placebo response rate was discounted from best supportive care, but not from the absolute response rates of apremilast or the TNF-alpha inhibitors used in the model. However, in the revised base case, the company had included a placebo response for best supportive care. The Committee agreed that inclusion of placebo response rates in the model was necessary and accepted this revision to the model.

4.19 The Committee noted that the company's original base case results were based on uncertain assumptions. It appreciated that the company had attempted to address this uncertainty by making several changes in its revised model (including equal levels of monitoring for apremilast and TNF-alpha inhibitors, a placebo response for best supportive care, and utility values derived from the apremilast trial), and also by presenting several exploratory analyses. However, most ICERs presented by the company were based on treatment sequences with an unequal number of treatments, which was not the Committee's preference (see section 4.11 and 4.19). The Committee therefore went on to consider the exploratory analyses presented by the ERG. The Committee noted that the ERG had based its analyses on the revised company base case and, therefore, as in the company revised base case, it accounted for several uncertainties in the original base case. Also, the ERG had used the Committee's preferred treatment sequences, with an equal number of active comparators before progression to best supportive care, for its exploratory analyses. The Committee concluded that the exploratory analyses presented by the ERG were the most appropriate for decision-making.

4.20 The Committee considered the results for apremilast as a treatment before TNF-alpha inhibitor therapy, using its preferred exploratory analyses from the ERG (see sections 4.11 and 4.17). The Committee noted that all the ERG's sequences in which apremilast was the first treatment in a sequence (after DMARDs) resulted in cost savings but also a QALY loss, resulting in ICERs that reflected 'savings per QALY lost'. For example, when comparing a sequence of apremilast, adalimumab, etanercept and best supportive care with adalimumab, etanercept, golimumab, and best supportive care, and when using the
Committees preferred assumption of some HAQ-DI progression for apremilast (at half the rate of that for best supportive care) there was a cost saving of £6739 in the apremilast sequence, but a QALY loss of −0.368 (see section 3.46), resulting in an ICER of £18,300 saved per QALY lost. The Committee considered this to be the most plausible scenario because it used its preferred assumptions, and also because the results were consistent with the clinical and cost data; that is, when compared with TNF-alpha inhibitors, apremilast cost less but was also the least effective active treatment. The Committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee was aware that psoriatic arthritis is a chronic and progressive condition, that patients want treatments that stop disease progression (see section 4.10), and that apremilast was the least effective treatment in the company analyses (see sections 3.8 to 3.12). Taking all of the above into account, the Committee agreed that the ICER for apremilast was not high enough to compensate for the clinical effectiveness that would be lost. It therefore concluded that apremilast was not a cost-effective option compared with TNF-alpha inhibitors for people with psoriatic arthritis that has responded inadequately to DMARDs.

4.21 The Committee considered whether there was any evidence to consider apremilast as a treatment after TNF-alpha inhibitor therapy, or for people who could not take TNF-alpha inhibitors. It noted that evidence in this area was limited. The available clinical effectiveness evidence for apremilast was mostly for a population who had not previously had TNF-alpha inhibitors. The cost-effectiveness evidence was limited because the company had rejected this possible positioning of apremilast, even though such comparisons (particularly with ustekinumab) were listed in the final scope issued by NICE. The company had presented 2 direct comparisons of apremilast with best supportive care (see section 3.44), and when assuming apremilast HAQ-DI progression at a rate half that of best supportive care, the ICER for apremilast was £21,700 per QALY gained. The Committee noted, however, that the company had not explored the analyses further because it did not consider best supportive care to be an appropriate comparator. Following the publication of ustekinumab for treating active psoriatic arthritis, and given the range of other treatments available for psoriatic arthritis, there are a number of other possible treatments used after TNF-alpha inhibitors that would be available before best supportive care, and
these had not been explored as comparators. The Committee also considered the ERG’s scenarios for apremilast used after TNF-alpha inhibitors, which included the Committee’s preferred model assumption of the same number of active treatments in each sequence. The Committee was aware of the ERG’s comments regarding the validity of its exploratory analyses (see section 3.46) and agreed that as these were the only scenarios presented for apremilast used after TNF-alpha inhibitors, they should be taken into account in its decision-making. The Committee noted that in all the ERG’s exploratory analyses the apremilast treatment sequence resulted in cost savings but a QALY loss, resulting in ICERS that reflected ‘savings per QALY lost’. For example, a treatment sequence in which apremilast replaced golimumab in a sequence of adalimumab, etanercept, golimumab and best supportive care, assuming HAQ-DI progression at a rate equal to half of best supportive care, resulted in a cost saving of £5343 and a QALY loss of −0.362, with an ICER of £14,800 saved per QALY lost. The Committee agreed that this was the most plausible scenario that had been presented because it used the Committee’s preferred assumptions about treatment sequences with an equal number of treatments and some HAQ-DI progression for apremilast, the results were consistent with the clinical and cost data (that is, when compared with TNF-alpha inhibitors, apremilast cost less but was also the least effective active treatment), and also because of the limited evidence presented by the company. The Committee agreed that the ICER for apremilast was not high enough to compensate for the clinical effectiveness that would be lost. It therefore concluded that apremilast could not be recommended as a treatment after TNF-alpha inhibitors. It was unable to make recommendations for its use when people cannot take TNF-alpha inhibitors, because of a lack of evidence for its use in these circumstances.

4.22 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 conclusion on clinical efficacy (see section 4.6 to 4.8) 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.
4.23 The Committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant for its consideration of the cost effectiveness of any of the technologies in this appraisal.

Summary of Appraisal Committee's key conclusions

<table>
<thead>
<tr>
<th>TA372</th>
<th>Appraisal title: Apremilast for treating active psoriatic arthritis</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusion</td>
<td></td>
<td></td>
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</tbody>
</table>

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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.

The Committee considered the results for apremilast as a treatment before TNF-alpha inhibitor therapy. It noted that its preferred analyses by the Evidence Review Group's (ERG) in which apremilast was the first treatment in a sequence (after DMARDs) resulted in cost savings, but also a QALY (quality adjusted life year) loss, with the most plausible ICER being £18,300 saved per QALY lost. The Committee noted that the ERG's results were consistent with the clinical and cost data; that is, when compared with tumour necrosis factor (TNF)-alpha inhibitors, apremilast cost less and was the least effective active treatment in the meta-analyses.

The Committee considered whether there was any evidence to consider apremilast as a treatment after TNF-alpha inhibitor therapy. It noted that evidence in this area was limited. The Committee noted that in all its preferred analyses by the ERG, the apremilast treatment sequence resulted in cost savings but a QALY loss, with the most plausible ICER being £14,800 saved per QALY lost.

The Committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee agreed that the most plausible ICERs of £18,300 and £14,800 saved per QALY lost for apremilast, given before or after TNF-alpha inhibitors respectively, were not high enough to compensate for the clinical effectiveness that would be lost. It therefore concluded that apremilast could not be recommended as a treatment either before or after TNF-alpha inhibitors. It was unable to make recommendations for its use when people cannot take TNF-alpha inhibitors, because of a lack of evidence for its use in these circumstances.

Current practice

| 1.1, 4.20, 4.21 |

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### Clinical need of patients, including the availability of alternative treatments

The Committee heard from patient experts 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 concluded that psoriatic arthritis substantially decreases quality of life.

The Committee heard from patient and clinical experts that there is an unmet need for treatments that offer a different mechanism of action to the TNF alpha inhibitors or that are administered orally, as with apremilast (a PDE4 inhibitor).

### The technology

<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>The Committee 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 conclusions on clinical efficacy the Committee considered that apremilast was not a step change in treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>What is the position of the treatment in the pathway of care for the condition?</strong></th>
<th>The Committee noted that after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and 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. The Committee was aware that apremilast had the same marketing authorisation as the currently recommended biological treatments, but that the company had stated that apremilast would be used before these treatments in clinical practice. The Committee concluded that it was possible that apremilast could be used as a treatment before TNF-alpha inhibitors, but that any use or positioning of apremilast would need to be supported by clinical and cost-effectiveness evidence.</th>
<th>4.2, 4.3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse reactions</strong></td>
<td>The Committee concluded that apremilast has an acceptable adverse event profile in people with active psoriatic arthritis.</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Evidence for clinical effectiveness</strong></td>
<td>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. The Committee considered the evidence from the company’s network meta-analysis that compared apremilast with TNF-alpha inhibitors in the total population, and also in people who had not had TNF-alpha inhibitors. 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.</td>
<td>4.6, 4.8</td>
</tr>
<tr>
<td><strong>Availability, nature and quality of evidence</strong></td>
<td>The Committee understood that treatment with a DMARD such as methotrexate, followed by TNF-alpha inhibitors in people who can take them, 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.</td>
<td>4.2</td>
</tr>
</tbody>
</table>
The Committee discussed the ERG’s concerns that the placebo responses for some outcomes were high which made it difficult to compare the relative efficacies of apremilast with the different comparators.

The Committee heard from the ERG that there were uncertainties about the PSA-002, PSA-003 and PSA-004 results because the trials were not blinded after 24 weeks and there were no stopping rules. The Committee was therefore concerned that in comparison with more objective measures of disease progression such as radiographic assessments, there was a higher possibility of bias.

The Committee further considered the lack of radiographic assessment in the apremilast trials. It accepted that it may be necessary to interpret radiographic evidence with caution, and that disease activity outcomes play an important role in functional capacity.

Because it is a new treatment, there is a lack of long-term clinical-effectiveness data for apremilast.

| Uncertainties generated by the evidence | The Committee discussed the ERG’s concerns that the placebo responses for some outcomes were high which made it difficult to compare the relative efficacies of apremilast with the different comparators. The Committee heard from the ERG that there were uncertainties about the PSA-002, PSA-003 and PSA-004 results because the trials were not blinded after 24 weeks and there were no stopping rules. The Committee was therefore concerned that in comparison with more objective measures of disease progression such as radiographic assessments, there was a higher possibility of bias. The Committee further considered the lack of radiographic assessment in the apremilast trials. It accepted that it may be necessary to interpret radiographic evidence with caution, and that disease activity outcomes play an important role in functional capacity. Because it is a new treatment, there is a lack of long-term clinical-effectiveness data for apremilast. |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | No specific Committee consideration. |

4.8, 4.9, 4.10
### Estimate of the size of the clinical effectiveness including strength of supporting evidence

The Committee heard that apremilast was associated with a similar American College of Rheumatology response criteria (ACR20 response) as methotrexate. It noted that apremilast was more effective than placebo for a number of skin and joint outcomes, and for associated conditions such as dactylitis and enthesitis. The Committee agreed that apremilast was a clinically effective treatment compared with placebo.

The Committee considered the evidence from the company’s network meta-analysis that compared apremilast with TNF-alpha inhibitors in the total population, and also in people who had not had TNF-alpha inhibitors. The Committee noted that the results showed that apremilast had a clinical benefit compared with placebo. However, apremilast demonstrated less clinical benefit than any of the TNF-alpha inhibitors, in either population. The Committee concluded that apremilast is not as clinically effective as the TNF-alpha inhibitors for treating psoriatic arthritis.

### Evidence for cost effectiveness

<table>
<thead>
<tr>
<th>Availability and nature of evidence</th>
<th>The Committee noted that the company’s revised model compared apremilast with treatment sequences rather than with a single comparator. The Committee accepted that the use of treatment sequences was a valid approach to modelling.</th>
</tr>
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</table>

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<table>
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<tr>
<th>Uncertainties around and plausibility of assumptions and inputs in the economic model</th>
<th>The Committee noted that the company had compared sequences with a different number of active treatments before best supportive care (3 for apremilast, 2 for the comparator group). The Committee agreed that, in clinical practice, patients would likely receive more than the 2 active treatments that patients were assumed to receive in the comparator group before they progressed to best supportive care. The Committee also understood that, assuming all other things were equal, replacing apremilast in the intervention group of the company’s revised base case with any of the TNF-alpha inhibitors would result in a QALY gain over the comparator sequence. The Committee concluded that in order to prevent the model being confounded by any QALY gain occurring only because of one group in the model having an extra active treatment, it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>The Committee noted that the utility values in the company’s revised base case were derived from the apremilast trial. The Committee was surprised at the estimates of utility, which appeared very low and similar to technologies for end of life conditions. However, the Committee agreed that the company had used a legitimate source for utility values by using the available trial data, and accepted the utility values for decision making. 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.</td>
</tr>
<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>No specific Committee consideration.</td>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>The Committee noted that HAQ-DI was a key driver of the economic model.</td>
</tr>
<tr>
<td></td>
<td>The Committee concluded that in order to prevent the model being confounded by any QALY gain occurring only because of one group in the model having an extra active treatment, it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence.</td>
</tr>
</tbody>
</table>
Most likely cost-effectiveness estimate (given as an ICER)

| Most likely cost-effectiveness estimate (given as an ICER) | The Committee noted that all the ERG’s sequences in which apremilast was the first treatment in a sequence (after DMARDs) resulted in cost savings, but also a QALY loss. For example, when comparing apremilast, adalimumab, etanercept and best supportive care with adalimumab, etanercept, golimumab, and best supportive care, and when using the Committees preferred assumption of some HAQ-DI progression for apremilast (at half the rate of best supportive care) there was a cost saving of £6739 in the apremilast sequence, but a QALY loss of -0.368, resulting in an ICER of £18,300 saved per QALY lost. The Committee considered this to be the most plausible scenario because it used its preferred assumptions, and also because the results were consistent with the clinical and cost data; that is, when compared with TNF-alpha inhibitors, apremilast cost less but was also the least effective active treatment.

The Committee considered whether there was any evidence to consider apremilast as a treatment after TNF-alpha inhibitor therapy. It noted that evidence in this area was limited. The Committee noted that in all exploratory analyses by the ERG, the apremilast treatment sequence resulted in cost savings but a QALY loss. For example, a treatment sequence in which apremilast replaced golimumab in a sequence of adalimumab, etanercept, golimumab and best supportive care (assuming HAQ-DI progression at a rate equal to half that of best supportive care) resulted in a cost saving of £5343, a QALY loss of −0.362, and an ICER of £14,800 saved per QALY lost. The Committee agreed that this was the most plausible scenario that had been presented because it used the Committee’s preferred assumptions about treatment sequences with an equal number of treatments and some HAQ-DI progression for apremilast, and also because of the limited evidence presented by the company.

The Committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee agreed that the most plausible ICERs of £18,300 | 4.20, 4.21 |
and £14,800 saved per QALY lost for apremilast, given before or after TNF-alpha inhibitors respectively, would not compensate for the clinical effectiveness that would be lost. It therefore concluded that apremilast could not be recommended as a treatment either before or after TNF-alpha inhibitors. It was unable to make recommendations for its use when people cannot take TNF-alpha inhibitors, because of a lack of evidence for its use in these circumstances.

<table>
<thead>
<tr>
<th>Additional factors taken into account</th>
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<tbody>
<tr>
<td>Patient access schemes (PPRS)</td>
</tr>
<tr>
<td>Not applicable.</td>
</tr>
<tr>
<td>End-of-life considerations</td>
</tr>
<tr>
<td>Not applicable.</td>
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<tr>
<td>Equalities considerations and social value judgements</td>
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<tr>
<td>Not applicable.</td>
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</tbody>
</table>

Apremilast for treating active psoriatic arthritis (TA372)

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Page 42 of 50
5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
December 2015
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

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Apremilast for treating active psoriatic arthritis (TA372)

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 Andrea Manca
Health Economist and Senior Research Fellow, University of York

Dr Suzanne Martin
Reader in Health Sciences

Dr Iain Miller
Founder & CEO, Health Strategies Group

Dr Paul Miller
Market Access Adviser

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr John Radford
GP, NHS Sheffield

Dr Claire Rothery
Research Fellow in Health Economics, University of York

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/Carl Prescott
Technical Leads

Fay McCracken/Nicola Hay/Fiona Pearce
Technical Advisers

Lori Farrar
Project Manager
7 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:


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. 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)
- 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 apremilast for treating active psoriatic arthritis by attending the initial Committee discussion and providing a written statement to the Committee. They were also 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
About this guidance

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

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

We have produced information for the public explaining this guidance. Information about the evidence it is based on is also available.

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

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

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

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Accreditation