NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Apremilast for treating active psoriatic arthritis

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

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

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

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

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

After consultation:

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

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

The key dates for this appraisal are:

Closing date for comments: 1 November 2016

Second appraisal committee meeting: 9 November 2016

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

1 Recommendations

1.1 Apremilast alone or in combination with disease-modifying antirheumatic drugs (DMARDs) is recommended within its marketing authorisation as an option for treating active psoriatic arthritis in adults, when:

- their disease has not responded to DMARDs or
- DMARDs are not tolerated and
- the company provides apremilast with the discount agreed in the patient access scheme.

2 The technology

Description of the technology	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).
Marketing authorisation	Apremilast 'alone or in combination with disease-modifying antirheumatic drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy'.
Adverse reactions	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.
Recommended dose and schedule	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).
Price	The price of apremilast is £550.00 for a 28 day pack (56×30 mg tablets) (excluding VAT; British National Formulary online, accessed September 2016). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of apremilast, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Celgene and a review of this submission by the evidence review group (ERG). This appraisal was a rapid review of the published NICE technology appraisal guidance on apremilast for treating psoriatic arthritis. It focused on cost-effectiveness

analyses using a patient access scheme agreement, which provides apremilast at a reduced cost. The discount is commercial in confidence. See the committee papers for full details of the rapid review evidence, and the history for full details of the evidence used for NICE's original technology appraisal guidance on apremilast for treating psoriatic arthritis. See section 4.24 onwards for the rapid review consideration

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 seriously affects 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 taking non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) such as

methotrexate, most people with non-responsive disease will have 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 PDE4 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 in June 2015, NICE 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 relatively 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 most 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 ACR20, with a response experienced by 37% of people having apremilast compared with 19% having placebo ($p \leq 0.0001$). The clinical experts noted that apremilast was associated with a similar ACR20 response to methotrexate. The committee 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 NICE technology appraisal 372 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 ARC50 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 NICE technology appraisal 372 section 3.8 to 3.12). The committee heard from the ERG that the methods used to identify both published and

unpublished studies for the network meta-analysis were appropriate, and the studies were mostly well reported. The committee discussed the ERG's concerns that the placebo responses (see NICE technology appraisal 372 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 committee concluded that apremilast is not as clinically effective as the TNF-alpha inhibitors for treating psoriatic arthritis.

4.9 The committee considered the HAQ-DI outcome used by the company to calculate functional capacity and to assess disease progression. It heard from the ERG that there were uncertainties about the results 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 NICE technology appraisal 372 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 NICE technology appraisal 372 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). 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 NICE technology appraisal 372

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 most 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 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 NICE technology appraisal 372 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 NICE technology appraisal 372 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 NICE technology appraisal 372 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 NICE technology appraisal 372 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 £5,343 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 sections 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

Rapid review

Positioning of apremilast

4.24 The committee noted that the company's rapid review submission had presented a base case for apremilast as a pre-TNF-alpha inhibitor treatment only, despite the committee previously stating that the clinical evidence did not support the use of apremilast before the more effective TNF-alpha inhibitors (section 4.10). The committee had also previously accepted that it was possible that in clinical practice, apremilast might be used before TNF-alpha inhibitors (section 4.3); for example, some patients may prefer an oral treatment and may therefore be willing to accept some reduced effectiveness. However, the committee agreed that any recommendation it made would be on the basis of whether apremilast could be considered a cost-effective treatment option alongside all other existing treatment options; it was not producing a treatment sequencing guideline. The committee discussed whether the company had presented enough analyses to fully consider the likely impact of apremilast, should it be recommended. It noted that the company had not explored the full treatment pathway in its rapid review submission, with most analyses limited to a maximum of 3 treatments in a sequence. However, the committee appreciated that the company had updated several assumptions in its base case to address committee concerns (for example, the base case now included an equal rather than uneven number of active treatments in each arm), and had also presented several new analyses which contributed to reducing the

uncertainties outlined in NICE technology appraisal guidance 372. These included the addition of direct head-to-head comparisons with several comparators from the scope, scenarios where apremilast was positioned after TNF-alpha inhibitors, and the addition of the scope comparator ustekinumab. The committee agreed that, in addition to the base case presented, it would have also preferred to see a company base case for apremilast as a post-TNF-alpha inhibitor treatment. However, it concluded that the company and ERG exploratory analyses helped to reduce uncertainty in the cost-effectiveness results.

HAQ-DI

4.25 The committee was aware that HAQ-DI was a principle uncertainty in the original company model for NICE technology appraisal 372. It noted and appreciated that although there was a lack of evidence to support the exact value, the company had modelled some HAQ-DI progression for apremilast (at a rate of 50% of best supportive care) in its revised analyses. Both the company and the ERG had also attempted to explore this uncertainty by using different rates of HAQ-DI progression for apremilast, and the committee heard from the company that it now had access to 3-year clinical trial data for apremilast, showing that HAQ-DI had been maintained for patients using apremilast. The committee concluded that the company had taken the correct approach by including some HAQ-DI progression for apremilast in its base case and that, in the absence of more robust evidence, the value used of 50% of the rate of best supportive care was a pragmatic assumption.

Modelled response to treatment

4.26 The committee noted that the modelled response to treatment was binary, with modelled patients achieving either response or no response, using PsARC (psoriatic arthritis response criteria, which assesses several joint and skin outcomes). The committee

considered whether this binary categorisation would accurately capture response to treatment, which may be more nuanced in clinical practice. It heard from the company that disease progression for psoriatic arthritis is driven by swollen joints. The committee also noted that the company had explored using ACR20 as a measure of response to treatment in its analyses, and this did not have a substantial effect on results. The committee concluded that the modelled response to treatment was imperfect, but appropriate for decision-making.

Declining effectiveness assumption

4.27 The committee noted that any TNF-alpha inhibitor given in a modelled treatment sequence after previous TNF-alpha inhibitor treatment was assumed to be less effective. The committee heard that the evidence for this was indirect. The committee concluded that although there was uncertainty about the declining effectiveness assumption for TNF-alpha inhibitors, it was plausible that the effectiveness of a TNF-alpha inhibitor could be affected by the use of a prior TNF-alpha inhibitor. The company also highlighted that this assumption did not affect any head-to-head analyses. The committee accepted this assumption for decision-making.

Most plausible ICERs

4.28 The committee discussed whether it could identify a most plausible ICER. It noted that the base-case ICER with the apremilast patient access scheme was £39,052 saved per QALY lost. The committee also considered the sensitivity and scenario analyses presented by both the company and the ERG. All showed that, as in the company's base case, using apremilast resulted in cost savings but a QALY loss. All were over £20,000 saved per QALY lost, and most were also over £30,000 saved per QALY lost. The committee agreed that the analyses that were under £30,000 saved per QALY

lost were not the most realistic scenarios and agreed that the inclusion of the apremilast patient access scheme had increased the cost savings for apremilast, such that they were at a more acceptable level given the QALYs that would be lost.

Biosimilars

4.29 The committee was aware that biosimilars for the comparators infliximab and etanercept are now available, and that the company had not included biosimilar infliximab despite its being a comparator in the scope. The committee considered what effect the inclusion of biosimilars could have had on the cost-effectiveness results. It agreed that the effect of modelling biosimilars was likely to be most pronounced if they were given before another TNF-alpha inhibitor (because the declining effectiveness assumption [see section 4.27] meant that treatment was likely to be shorter if the modelled patient had previously had a TNF-alpha inhibitor). The committee heard from the ERG that it had done some informal analyses which suggested that in the context of the base case (which did not include infliximab), adding biosimilar etanercept did not substantially change cost-effectiveness results. The committee was also aware that in direct head-to-head comparisons, apremilast demonstrated the highest cost-effectiveness results when compared with infliximab (the ICER was over £40,000 saved per QALY lost without the apremilast patient access scheme), so although the inclusion of biosimilar infliximab would worsen (that is, lower) the ICER for apremilast, the overall interpretation of the result was likely to be the same. The committee concluded that it would have preferred to have seen the inclusion of biosimilar infliximab, but that the cost-effectiveness results were still appropriate for decision-making.

Recommendation

4.30 The committee agreed that, because apremilast is a less effective treatment than the currently available treatment options (see section 4.8), it was particularly important to consider the possible consequences of a positive recommendation for individual patients. It stated that the addition of apremilast to the existing treatment pathway would mean patients would have access to an additional treatment with a different mechanism of action. Furthermore, the committee agreed that some patients may be willing to accept a certain level of reduced effectiveness because apremilast, unlike the TNF-alpha inhibitors and ustekinumab, is taken orally. The committee therefore agreed that apremilast could improve patient choice while also offering the opportunity of cost savings for the NHS (with cost savings at a level which was likely to compensate for any QALY gain that would be lost). It concluded that apremilast could be recommended as a cost-effective use of NHS resources.

4.31 The committee emphasised that apremilast should be seen as just one option in the context of a range of existing treatment options. The committee was aware that NICE technology appraisal guidance on etanercept, infliximab and adalimumab and golimumab for the treatment of psoriatic arthritis recommend that the least costly treatment option should be used first. However, the committee agreed that apremilast should not be used based on cost alone, because all clinical-effectiveness results showed it to be the least effective treatment. The committee agreed that the intention of its recommendation was to improve individual patient and clinician choice while also offering the chance of cost savings for the NHS. Apremilast in routine NHS practice should not be a barrier for access to existing treatments; patients and their clinicians should still have the choice of the full range of treatments, including the more expensive and more effective TNF-alpha inhibitors, if they are more clinically appropriate. The committee

concluded that the decision to use apremilast should not be made based on cost alone, and that individual patient factors, including patient needs and preferences, should also be taken into consideration.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
1.1 Apremilast alone or in combination with disease-modifying antirheumatic drugs (DMARDs) is recommended within its marketing authorisation as an option for treating active psoriatic arthritis in adults, when: • their disease has not responded to DMARDs or • DMARDs are not tolerated and • the company provides apremilast with the discount agreed in the patient access scheme. The committee noted that the base-case ICER with the apremilast patient access scheme was £39,052 saved per QALY lost. All exploratory analyses presented by both the company and the ERG also showed that using apremilast resulted in cost savings but a QALY loss. The committee stated that the addition of apremilast to the existing treatment pathway would mean patients would have access to an additional treatment with a different mechanism of action. Furthermore, the committee agreed that some patients may be willing to accept a certain level of reduced effectiveness because apremilast, unlike the TNF-alpha inhibitors and ustekinumab, is administered orally. The committee therefore agreed that apremilast could improve		1.1, 4.28, 4.30, 4.31

patient choice while also offering the opportunity of cost savings for the NHS (with cost savings likely to compensate for any QALY gain that would be lost). It concluded that apremilast could be recommended as a cost-effective use of NHS resources. The committee also concluded that the choice to use apremilast should not be made based on cost alone, because all clinical effectiveness results showed it to be the least effective treatment.		
Current practice		
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 seriously affects 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).	4.1, 4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	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.	4.22
What is the position of the treatment in the pathway of care for the condition?	The committee noted that after taking non-steroidal anti-inflammatory drugs (NSAIDs) and DMARDs, most people with non-responsive disease will have 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, for example some people may prefer an oral treatment and may therefore be willing to accept some reduced effectiveness, but that any use or positioning of apremilast would need to be supported by clinical- and cost-effectiveness evidence.	4.2, 4.3, 4.24

Adverse reactions	The committee concluded that apremilast has an acceptable adverse event profile in people with active psoriatic arthritis.	4.4
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	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.	4.6, 4.8
Relevance to general clinical practice in the NHS	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.	4.2, 4.24

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 compared 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.	4.8, 4.9, 4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No specific committee consideration.	–

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee heard that apremilast was associated with a similar 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.	4.6, 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The company base case compared treatment sequences with and without apremilast. The committee accepted that the use of treatment sequences was a valid approach to modelling	4.11

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that the company had not explored the full treatment pathway in its rapid review submission, with most analyses limited to a maximum of 3 treatments in a sequence. However, the committee appreciated that the company had updated several assumptions in its base case to address committee concerns (for example, the base case now included an equal rather than uneven number of active treatments in each arm), and had also presented several new analyses which contributed to reducing the uncertainties outlined in the previous appraisal of apremilast in this indication. These included the addition of direct head-to-head comparisons with several comparators from the scope, scenarios where apremilast was positioned after TNF-alpha inhibitors, and the addition of the scope comparator ustekinumab. The committee agreed that, in addition to the base case presented, it would have also preferred to see a company base case for apremilast as a post-TNF-alpha inhibitor treatment. However, it concluded that the company and ERG exploratory analyses helped to reduce uncertainty in the cost-effectiveness results.	4.24

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	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.	4.15
Are there specific groups of people for whom the technology is particularly cost effective?	No specific committee consideration.	–

What are the key drivers of cost effectiveness?	The committee noted that HAQ-DI was a principle driver of the economic model. It noted and appreciated that, although there was a lack of evidence to support the exact value, the company had modelled some HAQ-DI progression for apremilast (at a rate of 50% of best supportive care) in its revised analyses. Both the company and the ERG had also attempted to explore this uncertainty by using different rates of HAQ-DI progression for apremilast.	4.14, 4.25
Most likely cost-effectiveness estimate (given as an ICER)	The committee noted that the base-case ICER with the apremilast patient access scheme was £39,052 saved per QALY lost. The committee also considered the sensitivity and scenario analyses presented by both the company and the ERG. All showed that, as in the company's base case, using apremilast resulted in cost savings but a QALY loss. All company and ERG ICERs were over £20,000 saved per QALY lost. Most company and ERG ICERs were also over £30,000 saved per QALY lost. The committee agreed that the analyses that were under £30,000 saved per QALY lost were not the most realistic scenarios and agreed that the addition of the apremilast patient access scheme had increased the cost savings for apremilast so that they were at a level that could compensate for the QALYs that would be lost.	4.28
Additional factors taken into account		

Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of apremilast. The level of the discount is commercial in confidence.	–
End-of-life considerations	Not applicable.	–
Equalities considerations and social value judgements	Not applicable.	–

5 Implementation

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

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

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has psoriatic arthritis and the

doctor responsible for their care thinks that apremilast is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Celgene have agreed that apremilast will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

6 Review of guidance

6.1 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.

Professor Andrew Stevens
Chair, Appraisal committee
October 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

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

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.

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.

Carl Prescott
Technical lead

Nicola Hay
Technical adviser

Stephanie Yates
Project manager

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