NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Apremilast for treating active psoriatic arthritis (rapid review TA372) [ID1017]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:

    - **Celgene**
    - **British Society of Rheumatology**
    - **Psoriasis and Psoriatic Arthritis Alliance**
    - **Psoriasis Association**
    - **AbbVie**
    - **Merck Sharp & Dohme**
    - **Novartis Pharmaceuticals**

‘*No comment’ response received from British Association of Dermatologists, Department of Health and Pfizer*

3. **Comments on the Appraisal Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Apremilast for treating active psoriatic arthritis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Celgene	Has all relevant new evidence on the cost effectiveness been taken into account? Yes Are the conclusions on cost effectiveness a reasonable interpretation of the evidence? Yes Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes Celgene welcomes the draft positive recommendation for apremilast in active psoriatic arthritis (PsA) and considers that apremilast would represent a valuable addition to the current range of treatment options available to patients in England and Wales. PsA is a heterogeneous, chronic systemic inflammatory disease that has multiple signs and symptoms, including inflamed joints and entheses, as well as psoriasis, and can lead to reduced physical function and quality of life for patients.1-4 Consequently, the optimal treatment strategy in PsA is dependent on a number of factors and should be individualized based on individual patient factors, including patient needs and preferences. Apremilast, within its licensed indication, offers a clinically effective and cost-effective treatment option with a novel mode of action. Apremilast is a small molecule, oral alternative to injectable biologic therapies and does not require pre-screening for tuberculosis or routine laboratory monitoring. Treatment may result in reduced monitoring visits compared with biologic treatment resulting in a favorable impact on NHS resources and added patient convenience. As apremilast is orally administered, treatment may also result in a decreased need for intravenous (IV) clinics associated with those treatments administered by IV methods such as infliximab, thus moving patient care closer to home. Celgene considers that patients with PsA value having a range of available options and, in addition to increasing patient choice, Celgene agrees with the Committee that the inclusion of apremilast to the existing treatment pathway offers the potential for drug cost-savings to the NHS as noted in section 4.30 of the Appraisal Consultation Document (ACD).	Thank you for your response. Comments noted.

Consultee	Comment [sic]	Response
The Psoriasis and Psoriatic Arthritis Alliance	As an organisation that represents people affected by psoriasis and psoriatic arthritis, we support the opportunity for patients to get access to the latest therapies to alleviate their symptoms and limit disease progression. We also would like to see patients get better outcomes, fewer side effects and more convenient administration, therefore reducing the burden of being a patient, tied to frequent interventions, and dosage. We also acknowledge that the cost of treating each patient within the NHS has to be fair and equitable and any new treatment has to provide value for money and not have a detrimental effect on the service provided to others treated within the NHS. The merits of apremilast appear to be based on it being an oral medication and better than placebo, (although with similar responses to methotrexate), both of these could be seen as valid and useful to a patient when considering therapy for psoriatic arthritis, and of course we welcome the ability for patients to have further choice and options. Where we have concerns is potentially the chance that apremilast might delay access to more effective treatments at the same qualifying point within the pathway. I'm sure, as stated in the ACD, patients may be prepared to have a less effective drug in a format they feel is more suited to their health beliefs. Although if a patient's disease could be progressing, there needs to be some indication of when to move onto the next level of therapy, particularly given the lack of evidence around whether apremilast prevents radiographic progression. Psoriatic arthritis, unlike its skin component, is more likely to have a profound irreversible impact if allowed to progress, particularly once the damage to the joints has been done. I think it would be useful to provide a clear steer in the recommendations section 1.1 for both patients and clinicians to understand at which point apremilast is stopped. The clinical effectiveness suggests that 16-weeks is a point when ACR20 is reached versus placebo, therefore this would indicate that if not significantly exceeded, a further option should be offered.	Thank you for your comments. The committee agreed that it is important to ensure access to more effective treatments is not delayed. Please see FAD sections 4.30, 4.31 and 4.34. The committee concluded that its recommendation should specify that if an adequate response to apremilast is not observed at 16 weeks, treatment with apremilast should be stopped and other treatments considered. The FAD recommendation has been updated. Please see FAD section 1.2.

Consultee	Comment [sic]	Response
Psoriasis Association	The Psoriasis Association welcomes the positive recommendation of apremilast as an option for people with active psoriatic arthritis. Psoriasis Association members and supporters- and helpline enquirers-have expresses interest in the availability of apremilast. In particular, there is a clear need for a new oral alternative to those already available - allowing people with active psoriatic arthritis who cannot or do not wish to use injected medications a new option. Apremilast has a different mode of action to any conventional DMARD or biologic medication which is currently available for psoriatic arthritis, meaning that it also offers a genuine alternative for those who have not seen an acceptable response to other therapies. I have read the Appraisal Consultation Document and have no further comment to add, aside from asserting our support once again for the positive recommendation of apremilast as an option for people with active psoriatic arthritis.	Thank you for your response. Comments noted.
Department of Health	'no comment' response	Response noted.
British Association of Dermatologists	'no comment' response	Response noted.
British Society for Rheumatology 1	Psoriatic arthritis is a heterogeneous disease with diverse clinical manifestations. From a rheumatologic point of view it is appropriate to consider the condition as peripheral and axial arthritis. The peripheral arthritis can be usefully considered either oligoarticular (less than 4 joints) or polyarticular, although it should be accepted that this division is somewhat arbitrary. It is likely that the response to treatment differs between these sub-groups. For this reason it is difficult to design a single treatment algorithm to cover all aspects of the disease. The situation is complicated by the lack of evidence supporting the use of many of the so called 'disease modifying drugs' for use in psoriatic arthritis. Indeed, the drug that is the mainstay of treatment of psoriatic arthritis and the one that most rheumatologists first turn to at disease onset, methotrexate, has little support from randomised controlled trials. Further, methotrexate has no efficacy on axial disease. Nevertheless, there is sufficient evidence from observational studies, uncontrolled trials and physicians own experience for methotrexate to maintain a pivotal role in the treatment of peripheral psoriatic arthritis. Methotrexate is not without problems: patients often complain of nausea, hair thinning and both physicians and patients worry about hepatotoxicity, particularly in the overweight patients and those who consume moderate amount of alcohol. If methotrexate fails many physicians will be looking to use anti-TNF drugs, particularly if there are adverse prognostic factors. However, many European countries, including the UK as required by NICE Guidelines, advise the use of a second agent, such as sulfasalazine or leflunomide, before moving onto biologics.	Thank you for your response. Comments noted.

Consultee	Comment [sic]	Response
British Society for Rheumatology 2	How might apremilast fit into treatment algorithms? Although no head to head trials have been conducted, from an efficacy point of view it is clear that apremilast is less effective than TNF inhibitors in the treatment of both axial and peripheral arthritis of psoriatic arthritis. In such a case it might fit in as an alternative first systemic drug or as a second drug, or even in combination. The data from the studies so far show that it is marginally more efficacious than methotrexate on skin and joints. However, , unlike methotrexate, apremilast may have efficacy in the axial component, present in about 40% of cases of psoriatic arthritis. It is also worth noting that there are no safety concerns of hepatotoxicity in the short term studies with apremilast so this might confer advantages over methotrexate if a physician were considering treatment in a patient with risk factors for liver disease, a common problem in psoriatic arthritis. There are concerns about initial gastrointestinal tolerability which may play a part in the drugs' acceptability in practice. Long term familiarity and safety concerns will also play a part in prescribing patterns. It seems unlikely that apremilast will be positioned after TNFi in psoriatic arthritis. And people who fail, or are intolerant to, or who cannot take TNFi for other reasons, now have other drugs available to control their disease, such as secukinumab and ustekinumab. However, it is possible to envisage a scenario where a patient may have failed all these options, and still require a disease modifying drug – apremilast may be used in this situation.	Thank you for your response. Comments noted.
British Society for Rheumatology 3	From the data available so far apremilast may be a valuable addition the psoriasis and psoriatic arthritis treatment portfolio. However, although drugs such as apremilast seem to have a favourable side effect profile, both direct comparison with other drugs and long term studies are needed to complete the picture. Apremilast may have an advantage in women of child bearing potential in whom methotrexate is contra-indicated. And it would appear that apremilast can be used without concern in pre-existing liver disorders such as 'fatty liver'. It might also be worth noting that PDE4 inhibitors like apremilast could have a beneficial effect on depressive disorders, a not uncommon finding in patients with moderate to severe psoriasis and psoriatic arthritis. And it would seem that patients lose weight on this drug, a big advantage in a disease where obesity and the metabolic syndrome are very prevalent. Apremilast appears less effective than TNFi in psoriasis and is also probably less effective than ciclosporin. However, combination therapy with other immunomodulators may be an attractive proposition both to reduce the dose of the other immunomodulator and to reduce the side-effects of PDE4 inhibition. Drugs such as apremilast may also be used as maintenance therapy once remission has been induced by another drug.	Thank you for your response. Comments noted.

Comments received from clinical experts and patient experts

No comments received.

Comments received from commentators

Commentator	Comment [sic]	Response
Novartis 1	**Has all of the relevant evidence been taken into account?** No. We are concerned that the provisional recommendation is not aligned to that of previous technology appraisal guidance in psoriatic arthritis such as TA199 for etanercept, infliximab and adalimumab1; TA220 for golimumab2 and TA340 for ustekinumab.3 Furthermore, the wording of the recommendation suggests that apremilast is positioned earlier in the treatment pathway than the TNF-alpha inhibitors. This is contrary to the intent of the committee and could potentially result in a situation in which commissioners advocate use of apremilast prior to other treatments, purely on cost grounds, despite the fact that it is less effective. This could have the unintended effect of reducing, rather than expanding the number of treatment options available to patients with psoriatic arthritis.	Thank you for your comment. The committee discussed aligning the apremilast recommendation to the starting and stopping rules in previous psoriatic arthritis appraisals. Please see FAD sections 4.32 to 4.34. The FAD recommendation has been updated to reflect previous psoriatic arthritis appraisals. Please see FAD section 1.1 to 1.4.

Novartis 2	1) <u>Lack of clear wording around the positioning of apremilast</u> The provisional recommendation states that apremilast is recommended for patients when *"their disease has not responded to DMARDs or DMARDs are not tolerated*". This differs from the recommendation in TA199[1] in which specific TNF-alpha inhibitors are recommended where *"psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination".* The differences lie in the following three aspects*:* I. The recommendation does not explicitly specify the number of DMARDs that a patient must inadequately respond to in order to be eligible for apremilast. II. The recommendation does not explicitly require the trial of DMARDs to be '*adequate*' III. The recommendation appears to cover an additional group of patients who are not explicitly mentioned in TA199[1] and TA220[2]; patients in whom DMARDs are not tolerated. These differences suggest that apremilast is being positioned earlier and more broadly in the treatment pathway than TNF-alpha inhibitors (which are recommended after inadequate response to at least two DMARDs). This is at odds with the clinical and economic evidence assessed by the committee which does not support earlier and broader positioning of apremilast before TNF-alpha inhibitors. • The ACD states in section 4.3 that *"<u>any use or positioning of apremilast would need to be supported by clinical and cost-effectiveness evidence</u>, particularly because several effective treatment options are already recommended for psoriatic arthritis"*. • Section 4.10 of the ACD states *"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 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".* This opinion is reiterated in section 4.24 - *"the clinical evidence did not support the use of apremilast before the more effective TNF-alpha inhibitors".* • The economic analyses informing the committee's recommendation of apremilast are based on a model comparing a treatment sequence of apremilast followed by TNF-alpha inhibitors versus treatment sequences starting with TNF-alpha nhibitors. These analyses do not support positioning ahead of TNF-alpha inhibitors	Thank you for your comments. The committee discussed aligning the apremilast recommendation to previous psoriatic arthritis appraisals. Please see FAD sections 4.32 to 4.34. The FAD recommendation has been updated to include definition of previous treatment with DMARDs in line with previous appraisals. Please see FAD section 1.1.

Commentator	Comment [sic]	Response
	as the relevant comparators i.e. DMARDs have not been included. Therefore, apremilast should be positioned at the same point in the treatment pathway as the comparators (i.e. TNF-alpha inhibitors) against which it has been assessed. In addition, it is clear from section 4.24 of the ACD that the intent of the committee was to make apremilast available as an option alongside TNF-alpha inhibitors: *"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" [emphasis added]*. In concluding, the committee *"emphasised that apremilast should be seen as just one option in the context of a range of existing treatment options"* (Section 4.31). We understand the committee intends that apremilast should be an option for "*some patients*" who are "*willing to accept a certain level of reduced effectiveness*", with usage driven by patient preference. We consider that the wording of the provisional recommendation which appears to position apremilast ahead of TNF-alpha inhibitors in the treatment pathway, and for a broader population, is therefore contrary to the intent of the committee. We request that the apremilast guidance wording be aligned to that of TA199[1] i.e. to specify apremilast use after disease has not responded to adequate trials of at least 2 DMARDs, to ensure that patient choice is respected in the manner that the committee intended	
Novartis 3	2) <u>Lack of criteria around peripheral joint involvement and joint counts</u> Unlike existing NICE guidance in psoriatic arthritis,[1,2] the provisional recommendation does not specify that a patient should have peripheral arthritis, nor does it specify the number of tender joints (TJ) and swollen joints (SJ) a patient must have in order to be eligible for treatment. This is at odds with the main sources of clinical evidence (PSA-002[4], PSA-003[5], PSA-004[6]) used in support of the manufacturer's submission and considered by the committee. The inclusion criteria of these 3 studies required patients to have 3 or more tender joints and 3 or more swollen joints for at least 6 months (ACD, page 8). The mean joint counts in these studies were SJ>10 and TJ>20.[4-6] Therefore, the wording of the provisional recommendation is not supported by the clinical data and could be interpreted to suggest that apremilast is recommended in a broader population than TNF-alpha inhibitors. We request that the committee includes these criteria in the recommendation to ensure consistency with previous NICE guidance on TNF-alpha inhibitors for psoriatic arthritis[1], as per its intention described in point 2 above.	Thank you for your comment. The committee discussed aligning the apremilast recommendation to the starting rule in previous psoriatic arthritis appraisals. Please see FAD sections 4.32 to 4.34. The FAD recommendation has been updated to include definition of peripheral arthritis in line with previous appraisals. Please see FAD section 1.1.

Commentator	Comment [sic]	Response
Novartis 4	3) <u>Lack of criteria regarding response assessment and treatment discontinuation</u> The apremilast recommendation does not contain criteria regarding response assessment and treatment discontinuation in patients who fail to respond to apremilast. We are concerned this could lead to inappropriate long-term use of this less effective therapy. The most plausible ICERs found to be acceptable by the committee were based on the apremilast cost-effectiveness model that assessed response using the Psoriatic Arthritis Response Criteria (PsARC) at 16 weeks. Furthermore, existing NICE guidance in psoriatic arthritis[1,2] include clear recommendations regarding treatment discontinuation in non-responders at specified time points. We are concerned that the absence of a clear recommendation regarding response assessment and stopping criteria for apremilast could result in continued, unnecessary exposure to apremilast amongst patients who are not experiencing a clinically meaningful benefit. It is critical that stopping criteria be specified as there is lack of evidence that apremilast slows radiographic progression - *"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"* (section 4.10 of the ACD). We request that the committee includes a stopping criteria based on PsARC response, for patients who do not experience adequate clinical benefit with apremilast.	Thank you for your comment. The committee discussed aligning the apremilast recommendation to the previous psoriatic arthritis appraisals. Please see FAD sections 4.32 to 4.34. The FAD recommendation has been updated to state that treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response at 16 weeks. Please see FAD section 1.2.

Commentator	Comment [sic]	Response
Novartis 5	4) <u>Lack of wording to guide reader in interpreting the recommendation in the context of existing guidance</u> The apremilast ACD states that "*apremilast is a less effective treatment compared to biologic therapies*" (section 4.30), but offers cost-savings. Since the apremilast recommendation will be considered alongside existing NICE guidance (notably TA199[1]), it is important to consider this context. TA199[1] states that "*Treatment…should normally be started with the least expensive drug*". Subsequent NICE guidance (TA220[2] and TA340[3]) have cross-referred to the TA199[1] guidance. We would like to highlight that the TA199[1] statement regarding using the least expensive option, was included in guidance in which all three TNF-alpha inhibitors were considered to offer comparable clinical efficacy - section 4.3.3 of the TA199[1] FAD states *"the Committee concluded that there was not enough evidence to indicate clinically important differences in the effectiveness of individual TNF inhibitors in the treatment of psoriatic arthritis".* Given that the committee have concluded that apremilast offers reduced clinical efficacy versus TNF-alpha inhibitors, it will be important that the TA199[1] advice to use the least expensive option is not wrongly understood to apply to apremilast. We propose that clarification is required in Section 1 of the guidance, regarding apremilast offering lower clinical efficacy at a lower cost, which might be acceptable to some patients and clinicians under certain circumstances.	Thank you for your comment. The committee discussed and highlighted that it is important to ensure access to more effective treatments is not delayed after an inadequate response to apremilast. Please see FAD sections 4.30, 4.31, 4.34. The committee agreed that its recommendation should specify that if an adequate response to apremilast is not observed at 16 weeks, treatment with apremilast should be stopped and other treatments considered. The FAD recommendation has been updated. Please see FAD section 1.2.

Commentator	Comment [sic]	Response
Novartis 6	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No. Please see comments in response to the above question. There is no basis to recommend apremilast as a treatment option before TNF-alpha inhibitors due to the limited clinical and cost effectiveness evidence to support use in this population. Therefore, as outlined in our response to the previous question, we request the committee reviews the current apremilast guidance wording to ensure that it cannot be interpreted as a recommendation for long-term use of apremilast before TNF-alpha inhibitors, which would be contrary to the committee's intent outlined in paragraph 4.31 of the ACD: "*"the committee emphasised that apremilast should be seen as just one option in the context of a range of existing treatment options"*. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. Novartis is concerned that the provisional recommendation of apremilast for patients with active psoriatic arthritis may be interpreted as a pre TNF-alpha inhibitors recommendation, which would be inappropriate based on the committee's interpretation of the evidence that is described in the ACD. We request that the committee reviews the apremilast guidance wording to ensure it is aligned with that of TNF-alpha inhibitors, and cannot be interpreted as a recommendation for long-term use of apremilast earlier in the treatment pathway than the TNF-alpha inhibitors. Furthermore, we are concerned that there may be some confusion about current NHS practice and NICE guidance. Page 28 of the ACD (section on relevance to general clinical practice in the UK) states *'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…"*. This is not strictly true; the existing NICE guidance for the management of psoriatic arthritis (e.g. TA199[1]) explicitly states 'at least 2 DMARDs'. Therefore, assuming that established NHS practice is consistent with NICE guidance, patients should have trialled at least 2 standard DMARDs.	Thank you for your comments. The committee discussed the evidence available and concluded that it was suitable for decision making. Please see FAD Clinical (4.6-4.10) and Cost effectiveness sections (4.11-4.23), and the Rapid review specific sections (4.24-4.34). Thank you for your comment. The committee discussed aligning the apremilast recommendation to previous psoriatic arthritis appraisals. Please see FAD sections 4.32 to 4.34. The FAD recommendation has been updated to reflect previous psoriatic arthritis appraisals. Please see FAD section 1.1 to 1.4.
	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? Novartis does not have any comments in relation to the above potential equality issues.	Thank you for your response.

Commentator	Comment [sic]	Response
Novartis 7	In summary, Novartis recognises that under the revised assessment in 'rapid review', apremilast is deemed to be a cost effective use of NHS resources. However, as noted by the committee apremilast is associated with: 1. Lack of evidence showing inhibition of radiographic progression of PsA 2. Poor performance in all active comparator comparisons in terms of clinical effectiveness. The ACD describes clinical experts' concerns about positioning apremilast before TNF-alpha inhibitors due to the missed opportunity for inhibition of radiographic progression. Based on these factors the committee concludes that *"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".* Despite clear concerns from the clinical experts and the conclusions of the committee, the NICE ACD appears to recommend apremilast in a broader and potentially earlier patient population than TNF-alpha inhibitors, since there are no requirements for a minimum number of involved joints, no clear requirement for adequate trial of at least 2 prior DMARDs, and no clear discontinuation criteria. We request that this guidance be reassessed in the light of the guidance for TNF-alpha inhibitors in psoriatic arthritis[1].	Thank you for your comments. The committee discussed the evidence available and concluded that it was suitable for decision making. Please see FAD Clinical (4.6-4.10) and Cost effectiveness sections (4.11-4.23), and the Rapid review specific sections (4.24-4.34). The committee discussed aligning the apremilast recommendation to previous psoriatic arthritis appraisals. Please see FAD sections 4.32 to 4.34. The FAD recommendation has been updated to reflect previous psoriatic arthritis appraisals. Please see FAD section 1.1 to 1.4.
Pfizer	'no comment' response	Comment noted.

Commentator	Comment [sic]	Response
AbbVie 1	**1. Has all relevant new evidence on the cost effectiveness been taken into account?** AbbVie considers that the majority of the new relevant evidence has been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However there are some issues which AbbVie believes the Committee should take into consideration before reaching a final decision and these are outlined below: **Treatment sequencing** The new base case presented by the company did not explore the full treatment pathway with most analyses limited to a maximum of 3 treatments in a sequence. Also the company did not provide a scenario analysis for use of apremilast as a post-TNF-alpha inhibitor treatment. In Section 4.10 of the final appraisal determination (FAD) document in TA 372 it is states that "*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."* and 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."* AbbVie is of the opinion that all possible treatment sequences and scenarios should be considered and discussed by the Committee before a recommendation for apremilast in active psoriatic arthritis is made. **HAQ progression for apremilast** The company only explored the impact of alternative HAQ progression for apremilast as a pre-TNF-alpha inhibitor treatment. AbbVie believes that if apremilast is used as a post-TNF-alpha inhibitor treatment, alternative HAQ-DI progression for apremilast should be tested before a recommendation is made by the Committee. **Inclusion of biosimilar infliximab** The company did not include biosimilar infliximab in the base case despite it being a comparator in the scope. Although the ERG had done some informal analyses that suggested a limited impact of this on the cost-effectiveness results, AbbVie is of the opinion that a scenario analysis using biosimilar infliximab should be provided before a recommendation is made by the Committee.	Thank you for your comments. The committee concluded that the evidence available was suitable for decision making. Please see FAD cost effectiveness sections 4.11-4.23, and the rapid review specific sections *Positioning of apremilast* (4.24), *HAQ-DI* (4.25), and *Biosimilars* (4.29).

Commentator	Comment [sic]	Response
AbbVie 2	**2. Are the conclusions on cost effectiveness a reasonable interpretation of the evidence?** AbbVie considers the new analyses from the manufacturer and the ERG to provide, on the whole, a reasonable interpretation of the evidence. AbbVie does however have some concerns relating to some additional issues and uncertainties that were not fully addressed by the company. **Positioning of apremilast** The company's rapid review submission only presented a base case for apremilast as a pre-TNF-alpha inhibitor treatment, despite the committee previously stating that the clinical evidence did not support the use of apremilast before the more effective TNF-alpha inhibitors. AbbVie believes that as apremilast is a less effective treatment, with no radiographic evidence on disease progression, it should not be recommended, in absence of robust evidence, before a TNF-alpha inhibitor for the treatment of active psoriatic arthritis. AbbVie believes that this should be made clear in the NICE recommendation. **Decline in efficacy for TNF-alpha inhibitor** The company base case assumed that any TNF-alpha inhibitor given in a modelled treatment sequence after previous TNF-alpha inhibitor treatment was assumed to be less effective. This was done by applying a hazard ratio from an observational study in rheumatoid arthritis (Hyrich et al) to the efficacy of biologic therapies following first-line. The limitations of using this methodology and the uncertainty associated with this assumption on the cost effectiveness outputs was highlighted in the original ERG critique (Section 5.2.6.3, p71-73) and also in the more recent one (Section 6 pg20)	Thank you for your comments. The committee concluded that the evidence available was suitable for decision making. Please see FAD cost effectiveness sections 4.11-4.23, and the rapid review specific sections *Positioning of apremilast* (4.24) and *Declining effectiveness assumptions* (4.27).
AbbVie 3	**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** AbbVie considers that the Appraisal Committee has identified, discussed and based provisional recommendations in view of the key limitations in the manufacturer's economic model. However AbbVie also believes that there still remains high uncertainty especially in regards to cost effectiveness results when apremilast is positioned post TNF-alpha inhibitors.	Thank you for your comments. The committee discussed the evidence available and concluded that it was suitable for decision making. Please see FAD Clinical (4.6-4.10) and Cost effectiveness sections (4.11-4.23), and the Rapid review specific sections (4.24-4.34).

Commentator	Comment [sic]	Response
Merck Sharp & Dohme 1	• **Has all relevant new evidence on the cost effectiveness been taken into account?** It appears that all the relevant evidence on cost-effectiveness has been taken into account.	Thank you for your response. Comment noted.
Merck Sharp & Dohme 2	**Are the conclusions on cost effectiveness a reasonable interpretation of the evidence?** Apremilast appears to be cost-effective per QALY lost.	Thank you for your response. Comment noted.

Commentator	Comment [sic]	Response
Merck Sharp & Dohme 3	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No, the recommendations as they stand are not clear guidance to the NHS. *Recommendation 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" (P3; NICE, 2016)* There are two key issues that need to be addressed with the draft recommendations. Firstly, as the evidence assessed in the appraisal is for apremilast in combination with sequences of tumour necrosis factor (TNF)-alpha inhibitors, the recommendation should reflect those in Technology Appraisal 199 (TA 199) (NICE 210). Apremilast should only be considered after 'psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination'. Secondly, whilst the appraisal consultation document (ACD) does acknowledge that: • Apremilast was the least effective active treatment when compared with TNF-alpha inhibitors • Apremilast was cost-effective per QALY lost • Apremilast was the least expensive and the committee agreed that apremilast should not be used based on cost alone, as all clinical-effectiveness results revealed it to be the least effective treatment these factors should be acknowledged at the beginning of the ACD, as the issue of cost is in recommendation 1.2 of TA199 (NICE, 2010)	Thank you for your comments. The committee discussed aligning the apremilast recommendation to previous psoriatic arthritis appraisals. Please see FAD sections 4.32 to 4.34. The FAD recommendation has been updated to reflect the previous psoriatic arthritis appraisals. Please see FAD sections 1.1 to 1.4.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Health professional 1		I would strongly support the consultation document and the place of Apremilast in the treatment pathway. It's much needed extension of therapeutic armament desperately required to manage this often forgotten group of patients. It's novel, oral, safe and patient friendly. It does not require frequent monitoring. I've used it in over 20 patients so far with good results and when given options to patients, they would choose it over and above biologics at times in view of above attributes - true example of patient empowerment and shared decision making at its best. I also agree with the comments that PsA is a heterogeneous condition and biologics are an 'overkill' at times. This drug bridges that important gap and hence fulfills an unmet need for these patients. I look forward to having a positive TAG and being able to prescribe in my patients	Thank you for your response. Comments noted.
Health professional 2		The draft appears to take in to account the appropriate evidence and position apremilast appropriately. No obvious discrimination.	Thank you for your response. Comments noted.
Health professional 3		Apremilast is an important addition to the treatment armamentarium for patients with PsA. The recommendations made are appropriate and provide clear guidance for the use of the drug in routine clinical practice.	Thank you for your response. Comments noted.

Summary of comments received from members of the public

No comments received.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

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Single Technology Appraisal (rapid review)

Apremilast for treating active psoriatic arthritis (rapid review TA372) [ID1017]

Celgene comments on the appraisal consultation document

Has all relevant new evidence on the cost effectiveness been taken into account?
Yes

Are the conclusions on cost effectiveness a reasonable interpretation of the evidence?
Yes

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
Yes

Celgene welcomes the draft positive recommendation for apremilast in active psoriatic arthritis (PsA) and considers that apremilast would represent a valuable addition to the current range of treatment options available to patients in England and Wales.

PsA is a heterogeneous, chronic systemic inflammatory disease that has multiple signs and symptoms, including inflamed joints and entheses, as well as psoriasis, and can lead to reduced physical function and quality of life for patients.[1-4] Consequently, the optimal treatment strategy in PsA is dependent on a number of factors and should be individualized based on individual patient factors, including patient needs and preferences.

Apremilast, within its licensed indication, offers a clinically effective and cost-effective treatment option with a novel mode of action. Apremilast is a small molecule, oral alternative to injectable biologic therapies and does not require pre-screening for tuberculosis or routine laboratory monitoring. Treatment may result in reduced monitoring visits compared with biologic treatment resulting in a favorable impact on NHS resources and added patient convenience. As apremilast is orally administered, treatment may also result in a decreased need for intravenous (IV) clinics associated with those treatments administered by IV methods such as infliximab, thus moving patient care closer to home.

Celgene considers that patients with PsA value having a range of available options and, in addition to increasing patient choice, Celgene agrees with the Committee that the inclusion of apremilast to the existing treatment pathway offers the potential for drug cost-savings to the NHS as noted in section 4.30 of the Appraisal Consultation Document (ACD).

References

1. Lloyd P, Ryan C, Menter A. Psoriatic arthritis: an update. Arthritis. 2012;2012:176298.
2. Singh JA, Strand V. Spondyloarthritis is associated with poor function and physical health-related quality of life. J Rheumatol. 2009;36:1012-1020.
3. Tillett W, de-Vries C, McHugh NJ. Work disability in psoriatic arthritis: a systematic review. Rheumatology (Oxford). 2012;51:275-283.
4. Strand V, Fiorentino D, Hu C, et al. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. Health Qual Life Outcomes. 2013;11:82.

The British Society for Rheumatology

Please find below the British Society for Rheumatology's response to the appraisal consultation document (ACD) for the Single Technology Appraisal (rapid review) on apremilast for treating active psoriatic arthritis (TA372).

Psoriatic arthritis is a heterogeneous disease with diverse clinical manifestations. From a rheumatologic point of view it is appropriate to consider the condition as peripheral and axial arthritis. The peripheral arthritis can be usefully considered either oligoarticular (less than 4 joints) or polyarticular, although it should be accepted that this division is somewhat arbitrary. It is likely that the response to treatment differs between these sub-groups. For this reason it is difficult to design a single treatment algorithm to cover all aspects of the disease. The situation is complicated by the lack of evidence supporting the use of many of the so called 'disease modifying drugs' for use in psoriatic arthritis. Indeed, the drug that is the mainstay of treatment of psoriatic arthritis and the one that most rheumatologists first turn to at disease onset, methotrexate, has little support from randomised controlled trials. Further, methotrexate has no efficacy on axial disease. Nevertheless, there is sufficient evidence from observational studies, uncontrolled trials and physicians own experience for methotrexate to maintain a pivotal role in the treatment of peripheral psoriatic arthritis. Methotrexate is not without problems: patients often complain of nausea, hair thinning and both physicians and patients worry about hepatotoxicity, particularly in the overweight patients and those who consume moderate amount of alcohol. If methotrexate fails many physicians will be looking to use anti-TNF drugs, particularly if there are adverse prognostic factors. However, many European countries, including the UK as required by NICE Guidelines, advise the use of a second agent, such as sulfasalazine or leflunomide, before moving onto biologics.

How might apremilast fit into treatment algorithms? Although no head to head trials have been conducted, from an efficacy point of view it is clear that apremilast is less effective than TNF inhibitors in the treatment of both axial and peripheral arthritis of psoriatic arthritis. In such a case it might fit in as an alternative first systemic drug or as a second drug, or even in combination. The data from the studies so far show that it is marginally more efficacious than methotrexate on skin and joints. However, , unlike methotrexate, apremilast may have efficacy in the axial component, present in about 40% of cases of psoriatic arthritis. It is also worth noting that there are no safety concerns of hepatotoxicity in the short term studies with apremilast so this might confer advantages over methotrexate if a physician were considering treatment in a patient with risk factors for liver disease, a common problem in psoriatic arthritis. There are concerns about initial gastrointestinal tolerability which may play a part in the drugs' acceptability in practice. Long term familiarity and safety concerns will also play a part in prescribing patterns. It seems unlikely that apremilast will be positioned after TNFi in psoriatic arthritis. And people who fail, or are intolerant to, or who cannot take TNFi for other reasons, now have other drugs available to control their disease, such as secukinumab and ustekinumab. However, it is possible to envisage a scenario where a patient may have failed all these options, and still require a disease modifying drug – apremilast may be used in this situation.

From the data available so far apremilast may be a valuable addition the psoriasis and psoriatic arthritis treatment portfolio. However, although drugs such as apremilast seem to have a favourable side effect profile, both direct comparison with other drugs and long term studies are needed to complete the picture. Apremilast may have an advantage in women of child bearing potential in whom methotrexate is contra-indicated. And it would appear that apremilast can be used without concern in pre-existing liver disorders such as 'fatty liver'. It might also be worth noting that PDE4 inhibitors like apremilast could have a beneficial effect on depressive disorders, a not uncommon finding in patients with moderate to severe psoriasis and psoriatic arthritis. And it would seem that patients lose weight on this drug, a big advantage in a disease where obesity and the metabolic syndrome are very prevalent. Apremilast appears less effective than TNFi in psoriasis and is also probably less effective than ciclosporin. However, combination therapy with other immunomodulators may be an attractive proposition both to reduce the dose of the other immunomodulator and to reduce the side-effects of PDE4 inhibition. Drugs such as apremilast may also be used as maintenance therapy once remission has been induced by another drug.

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14 October 2016

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Dear Meindert

Apremilast for treating active psoriatic arthritis (rapid review TA372) [ID1017]
Appraisal consultation document

Thank you for the opportunity to comment on the above review document.

As an organisation that represents people affected by psoriasis and psoriatic arthritis, we support the opportunity for patients to get access to the latest therapies to alleviate their symptoms and limit disease progression. We also would like to see patients get better outcomes, fewer side effects and more convenient administration, therefore reducing the burden of being a patient, tied to frequent interventions, and dosage.

We also acknowledge that the cost of treating each patient within the NHS has to be fair and equitable and any new treatment has to provide value for money and not have a detrimental effect on the service provided to others treated within the NHS.

The merits of apremilast appear to be based on it being an oral medication and better than placebo, (although with similar responses to methotrexate), both of these could be seen as valid and useful to a patient when considering therapy for psoriatic arthritis, and of course we welcome the ability for patients to have further choice and options.

Where we have concerns is potentially the chance that apremilast might delay access to more effective treatments at the same qualifying point within the pathway. I'm sure, as stated in the ACD, patients may be prepared to have a less effective drug in a format they feel is more suited to their health beliefs. Although if a patient's disease could be progressing, there needs to be some indication of when to move onto the next level of therapy, particularly given the lack of evidence around whether apremilast prevents radiographic progression. Psoriatic arthritis, unlike its skin component, is more likely to have a profound irreversible impact if allowed to progress, particularly once the damage to the joints has been done.

I think it would be useful to provide a clear steer in the recommendations section 1.1 for both patients and clinicians to understand at which point apremilast is stopped. The clinical effectiveness suggests that 16-weeks is a point when ACR20 is reached versus placebo, therefore this would indicate that if not significantly exceeded, a further option should be offered.

Yours sincerely

[redacted]

26th October 2016

Apremilast for treating active psoriatic arthritis: Appraisal Consultation Document

To whom it may concern,

The Psoriasis Association welcomes the positive recommendation of apremilast as an option for people with active psoriatic arthritis.

Psoriasis Association members and supporters- and helpline enquirers- have expressed interest in the availability of apremilast. In particular, there is a clear need for a new oral alternative to those already available – allowing people with active psoriatic arthritis who cannot or do not wish to use injected medications a new option. Apremilast has a different mode of action to any conventional DMARD or biologic medication which is currently available for psoriatic arthritis, meaning that it also offers a genuine alternative for those who have not seen an acceptable response to other therapies.

I have read the Appraisal Consultation Document and have no further comment to add, aside from asserting our support once again for the positive recommendation of apremilast as an option for people with active psoriatic arthritis.

Yours faithfully,

[redacted]

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Single Technology Appraisal

Apremilast for treating active psoriatic arthritis

(rapid review TA372) [ID1017]

AbbVie's Response to the Appraisal Consultation Document

Dear Meindert

Please find below AbbVie's response to the Appraisal Consultation Document (ACD) of Apremilast for treating active psoriatic arthritis (rapid review TA372) [ID1017].

1. Has all relevant new evidence on the cost effectiveness been taken into account?

AbbVie considers that the majority of the new relevant evidence has been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However there are some issues which AbbVie believes the Committee should take into consideration before reaching a final decision and these are outlined below:

Treatment sequencing

The new base case presented by the company did not explore the full treatment pathway with most analyses limited to a maximum of 3 treatments in a sequence. Also the company did not provide a scenario analysis for use of apremilast as a post-TNF-alpha inhibitor treatment. In Section 4.10 of the final appraisal determination (FAD) document in TA 372 it is states that "*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."* and 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."* AbbVie is of the opinion that all possible treatment sequences and scenarios should be considered and discussed by the Committee before a recommendation for apremilast in active psoriatic arthritis is made.

HAQ progression for apremilast

The company only explored the impact of alternative HAQ progression for apremilast as a pre-TNF-alpha inhibitor treatment. AbbVie believes that if apremilast is used as a post-TNF-alpha inhibitor treatment, alternative HAQ-DI progression for apremilast should be tested before a recommendation is made by the Committee.

Inclusion of biosimilar infliximab

The company did not include biosimilar infliximab in the base case despite it being a comparator in the scope. Although the ERG had done some informal analyses that suggested a limited impact of this on the cost-effectiveness results, AbbVie is of the opinion that a scenario analysis using biosimilar infliximab should be provided before a recommendation is made by the Committee.

2. Are the conclusions on cost effectiveness a reasonable interpretation of the evidence?

AbbVie considers the new analyses from the manufacturer and the ERG to provide, on the whole, a reasonable interpretation of the evidence. AbbVie does however have some concerns relating to some additional issues and uncertainties that were not fully addressed by the company.

Positioning of apremilast

The company's rapid review submission only presented a base case for apremilast as a pre-TNF-alpha inhibitor treatment, despite the committee previously stating that the clinical evidence did not support the use of apremilast before the more effective TNF-alpha inhibitors. AbbVie believes that as apremilast is a less effective treatment, with no radiographic evidence on disease progression, it should not be recommended, in absence of robust evidence, before a TNF-alpha inhibitor for the

treatment of active psoriatic arthritis. AbbVie believes that this should be made clear in the NICE recommendation.

Decline in efficacy for TNF-alpha inhibitor

The company base case assumed that any TNF-alpha inhibitor given in a modelled treatment sequence after previous TNF-alpha inhibitor treatment was assumed to be less effective. This was done by applying a hazard ratio from an observational study in rheumatoid arthritis (Hyrich et al) to the efficacy of biologic therapies following first-line. The limitations of using this methodology and the uncertainty associated with this assumption on the cost effectiveness outputs was highlighted in the original ERG critique (Section 5.2.6.3, p71-73) and also in the more recent one (Section 6 pg20).

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

AbbVie considers that the Appraisal Committee has identified, discussed and based provisional recommendations in view of the key limitations in the manufacturer's economic model. However AbbVie also believes that there still remains high uncertainty especially in regards to cost effectiveness results when apremilast is positioned post TNF-alpha inhibitors.

Merck Sharp & Dohme Limited's comments on the Apremilast Appraisal Consultation document

- **Has all relevant new evidence on the cost effectiveness been taken into account?**

It appears that all the relevant evidence on cost-effectiveness has been taken into account.

- **Are the conclusions on cost effectiveness a reasonable interpretation of the evidence?**

Apremilast appears to be cost-effective per QALY lost.

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

No, the recommendations as they stand are not clear guidance to the NHS.

> *Recommendation 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" (P3; NICE, 2016)*

There are two key issues that need to be addressed with the draft recommendations. Firstly, as the evidence assessed in the appraisal is for apremilast in combination with sequences of tumour necrosis factor (TNF)-alpha inhibitors, the recommendation should reflect those in Technology Appraisal 199 (TA 199) (NICE 210). Apremilast should only be considered after 'psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination'.

Secondly, whilst the appraisal consultation document (ACD) does acknowledge that:

- Apremilast was the least effective active treatment when compared with TNF-alpha inhibitors
- Apremilast was cost-effective per QALY lost
- Apremilast was the least expensive and the committee agreed that apremilast should not be used based on cost alone, as all clinical-effectiveness results revealed it to be the least effective treatment

these factors should be acknowledged at the beginning of the ACD, as the issue of cost is in recommendation 1.2 of TA199 (NICE, 2010)

References

NICE (2110). *Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis Technology appraisal guidance*. NICE. Available online: https://www.nice.org.uk/guidance/ta199

NICE (2016). *Appraisal consultation document – apremilast for treating active psoriatic arthritis*. NICE.

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1st November 2016

Dear Sir/Madam,

Re: Apremilast for treating active psoriatic arthritis (rapid review of TA372) [ID1017] – Appraisal Consultation Document

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal.

This document answers the four questions posed by NICE on page 1 of the ACD.

Has all of the relevant evidence been taken into account?

No. We are concerned that the provisional recommendation is not aligned to that of previous technology appraisal guidance in psoriatic arthritis such as TA199 for etanercept, infliximab and adalimumab[1]; TA220 for golimumab[2] and TA340 for ustekinumab.[3] Furthermore, the wording of the recommendation suggests that apremilast is positioned earlier in the treatment pathway than the TNF-alpha inhibitors. This is contrary to the intent of the committee and could potentially result in a situation in which commissioners advocate use of apremilast prior to other treatments, purely on cost grounds, despite the fact that it is less effective. This could have the unintended effect of reducing, rather than expanding the number of treatment options available to patients with psoriatic arthritis.

Our concerns are as follows:

1) Lack of clear wording around the positioning of apremilast

The provisional recommendation states that apremilast is recommended for patients when *"their disease has not responded to DMARDs or DMARDs are not tolerated*". This differs from the recommendation in TA199[1] in which specific TNF-alpha inhibitors are recommended where *"psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination".*

The differences lie in the following three aspects*:*

I. The recommendation does not explicitly specify the number of DMARDs that a patient must inadequately respond to in order to be eligible for apremilast.
II. The recommendation does not explicitly require the trial of DMARDs to be '*adequate*'
III. The recommendation appears to cover an additional group of patients who are not explicitly mentioned in TA199[1] and TA220[2]; patients in whom DMARDs are not tolerated.

These differences suggest that apremilast is being positioned earlier and more broadly in the treatment pathway than TNF-alpha inhibitors (which are recommended after inadequate response to at least two DMARDs).

This is at odds with the clinical and economic evidence assessed by the committee which does not support earlier and broader positioning of apremilast before TNF-alpha inhibitors.

- The ACD states in section 4.3 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"*.

- Section 4.10 of the ACD states *"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 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".*

  This opinion is reiterated in section 4.24 - *"the clinical evidence did not support the use of apremilast before the more effective TNF-alpha inhibitors".*

- The economic analyses informing the committee's recommendation of apremilast are based on a model comparing a treatment sequence of apremilast followed by TNF-alpha inhibitors versus treatment sequences starting with TNF-alpha inhibitors. These analyses do not support positioning ahead of TNF-alpha inhibitors as the relevant comparators i.e. DMARDs have not been included. Therefore, apremilast should be positioned at the same point in the treatment pathway as the comparators (i.e. TNF-alpha inhibitors) against which it has been assessed.

In addition, it is clear from section 4.24 of the ACD that the intent of the committee was to make apremilast available as an option alongside TNF-alpha inhibitors: *"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" [emphasis added]*. In concluding, the committee *"emphasised that apremilast should be seen as just one option in the context of a range of existing treatment options"* (Section 4.31).

We understand the committee intends that apremilast should be an option for "*some patients*" who are "*willing to accept a certain level of reduced effectiveness*", with usage driven by patient preference. We consider that the wording of the provisional recommendation which appears to position apremilast ahead of TNF-alpha inhibitors in the treatment pathway, and for a broader population, is therefore contrary to the intent of the committee.

We request that the apremilast guidance wording be aligned to that of TA199[1] i.e. to specify apremilast use after disease has not responded to adequate trials of at least 2 DMARDs, to ensure that patient choice is respected in the manner that the committee intended.

2) Lack of criteria around peripheral joint involvement and joint counts

Unlike existing NICE guidance in psoriatic arthritis,[1,2] the provisional recommendation does not specify that a patient should have peripheral arthritis, nor does it specify the number of tender joints (TJ) and swollen joints (SJ) a patient must have in order to be eligible for treatment. This is at odds with the main sources of clinical evidence (PSA-002[4], PSA-003[5], PSA-004[6]) used in support of the manufacturer's submission and considered by the committee. The inclusion criteria of these 3 studies required patients to have 3 or more tender joints and 3 or more swollen joints for at least 6 months (ACD, page 8). The mean joint counts in these studies were SJ>10 and TJ>20.[4-6] Therefore, the wording of the provisional recommendation is not supported by the clinical data and could be interpreted to suggest that apremilast is recommended in a broader population than TNF-alpha inhibitors.

We request that the committee includes these criteria in the recommendation to ensure consistency with previous NICE guidance on TNF-alpha inhibitors for psoriatic arthritis[1], as per its intention described in point 2 above.

3) Lack of criteria regarding response assessment and treatment discontinuation

The apremilast recommendation does not contain criteria regarding response assessment and treatment discontinuation in patients who fail to respond to apremilast. We are concerned this could lead to inappropriate long-term use of this less effective therapy.

The most plausible ICERs found to be acceptable by the committee were based on the apremilast cost-effectiveness model that assessed response using the Psoriatic Arthritis Response Criteria (PsARC) at 16 weeks. Furthermore, existing NICE guidance in psoriatic arthritis[1,2] include clear recommendations regarding treatment discontinuation in non-responders at specified time points.

We are concerned that the absence of a clear recommendation regarding response assessment and stopping criteria for apremilast could result in continued, unnecessary exposure to apremilast amongst patients who are not experiencing a clinically meaningful benefit. It is critical that stopping criteria be specified as there is lack of evidence that apremilast slows radiographic progression - *"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"* (section 4.10 of the ACD).

We request that the committee includes a stopping criteria based on PsARC response, for patients who do not experience adequate clinical benefit with apremilast.

4) Lack of wording to guide reader in interpreting the recommendation in the context of existing guidance

The apremilast ACD states that "*apremilast is a less effective treatment compared to biologic therapies*" (section 4.30), but offers cost-savings. Since the apremilast recommendation will be considered alongside existing NICE guidance (notably TA199[1]), it is important to consider this context.

TA199[1] states that "*Treatment…should normally be started with the least expensive drug*". Subsequent NICE guidance (TA220[2] and TA340[3]) have cross-referred to the TA199[1] guidance. We would like to highlight that the TA199[1] statement regarding using the least expensive option, was included in guidance in which all three TNF-alpha inhibitors were considered to offer comparable clinical efficacy - section 4.3.3 of the TA199[1] FAD states *"the Committee concluded that there was not enough evidence to indicate clinically important differences in the effectiveness of individual TNF inhibitors in the treatment of psoriatic arthritis".*

Given that the committee have concluded that apremilast offers reduced clinical efficacy versus TNF-alpha inhibitors, it will be important that the TA199[1] advice to use the least expensive option is not wrongly understood to apply to apremilast.

We propose that clarification is required in Section 1 of the guidance, regarding apremilast offering lower clinical efficacy at a lower cost, which might be acceptable to some patients and clinicians under certain circumstances.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. Please see comments in response to the above question.

There is no basis to recommend apremilast as a treatment option before TNF-alpha inhibitors due to the limited clinical and cost effectiveness evidence to support use in this population. Therefore, as outlined in our response to the previous question, we request the committee reviews the current apremilast guidance wording to ensure that it cannot be interpreted as a recommendation for long-term use of apremilast before TNF-alpha inhibitors, which would be contrary to the committee's intent outlined in paragraph 4.31 of the ACD: "*"the committee emphasised that apremilast should be seen as just one option in the context of a range of existing treatment options"*.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No. Novartis is concerned that the provisional recommendation of apremilast for patients with active psoriatic arthritis may be interpreted as a pre TNF-alpha inhibitors recommendation, which would be inappropriate based on the committee's interpretation of the evidence that is described in the ACD. We request that the committee reviews the apremilast guidance wording to ensure it is aligned with that of TNF-alpha inhibitors, and cannot be interpreted as a recommendation for long-term use of apremilast earlier in the treatment pathway than the TNF-alpha inhibitors.

Furthermore, we are concerned that there may be some confusion about current NHS practice and NICE guidance. Page 28 of the ACD (section on relevance to general clinical practice in the UK) states *'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…".* This is not strictly true; the existing NICE guidance for the management of psoriatic arthritis (e.g. TA199[1]) explicitly states 'at least 2 DMARDs'. Therefore, assuming that established NHS practice is consistent with NICE guidance, patients should have trialled at least 2 standard DMARDs.

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?

Novartis does not have any comments in relation to the above potential equality issues.

In summary, Novartis recognises that under the revised assessment in 'rapid review', apremilast is deemed to be a cost effective use of NHS resources. However, as noted by the committee apremilast is associated with:

1. Lack of evidence showing inhibition of radiographic progression of PsA
2. Poor performance in all active comparator comparisons in terms of clinical effectiveness.

The ACD describes clinical experts' concerns about positioning apremilast before TNF-alpha inhibitors due to the missed opportunity for inhibition of radiographic progression. Based on these factors the committee concludes that *"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".*

Despite clear concerns from the clinical experts and the conclusions of the committee, the NICE ACD appears to recommend apremilast in a broader and potentially earlier patient population than TNF-alpha inhibitors, since there are no requirements for a minimum number of involved joints, no clear requirement for adequate trial of at least 2 prior DMARDs, and no clear discontinuation criteria.

We request that this guidance be reassessed in the light of the guidance for TNF-alpha inhibitors in psoriatic arthritis[1].

I hope that our comments are of value. If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

[redacted]
Novartis Pharmaceuticals UK Ltd

References

1. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance (TA199). Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (2010).
2. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance (TA220). Golimumab for the treatment of psoriatic arthritis (2011).
3. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance (TA340). Ustekinumab for treating active psoriatic arthritis (rapid review of technology appraisal guidance 313) (2015).
4. Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van Den Bosch F, Marzo-Ortega H, Feist E, Shah K, Hu CC, Stevens RM, Poder A. A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. The Journal of Rheumatology. 2016.vol.43 no.91724-1734
5. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, Stevens RM, Vessey A, Zhan X, Bird P. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis. 2016 Jun;75(6):1065-73.
6. Wells A, Edwards C, Adebajo AO, Kivitz AJ, Bird P, Shah K, Hu C, Stevens RM, Aelion JA. Palace 4, A Phase 3, Randomized, Controlled TRIAL of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, for Treatment of Psoriatic Arthritis: Long-Term (52-WEEK) Improvements in Physical Function. Ann Rheum Dis 2014;73:732

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Consultant Rheumatologist
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I would strongly support the consultation document and the place of Apremilast in the treatment pathway. It's much needed extension of therapeutic armament desperately required to manage this often forgotten group of patients. It's novel, oral, safe and patient friendly. It does not require frequent monitoring.

I've used it in over 20 patients so far with good results and when given options to patients, they would choose it over and above biologics at times in view of above attributes - true example of patient empowerment and shared decision making at its best.

I also agree with the comments that PsA is a heterogeneous condition and biologics are an 'overkill' at times. This drug bridges that important gap and hence fulfills an unmet need for these patients.

I look forward to having a positive TAG and being able to prescribe in my patients.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Rheumatologist
Other role	
Organisation	
Location	England
Conflict	Disclosure: Research funding from Celgene
Notes	
Comments on individual sections of the ACD:	

The draft appears to take in to account the appropriate evidence and position apremilast appropriately. No obvious discrimination.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant Rheumatologist
Other role	
Organisation	
Location	England
Conflict	Disclosure: I have received speaker fees from Celgene
Notes	
Comments on individual sections of the ACD: Apremilast is an important addition to the treatment armamentarium for patients with PsA. The recommendations made are appropriate and provide clear guidance for the use of the drug in routine clinical practice.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	