NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Apremilast moderate to severe - psoriasis (rapid review of TA368) [ID987]

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
   - Psoriasis Association
   - Psoriasis and Psoriatic Arthritis Alliance
   - British Association of Dermatologists
   - Abbvie
   - Janssen
   - Merck Sharp and Dohme
   - Novartis

   The Department of Health indicated that they had no comments

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 moderate to severe plaque psoriasis

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.

Confidential until publication

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	Response
Celgene	Celgene welcomes the draft positive recommendation for apremilast in moderate to severe chronic plaque psoriasis and considers that apremilast would represent a valuable addition to the current range of treatment options available to patients in England and Wales. Severe psoriasis is a multi-faceted condition with a significant psychosocial impact which substantially decreases quality of life. The optimal treatment strategy in psoriasis is dependent on multiple factors and can be highly individualized based on individual patient needs. Apremilast offers an additional, clinically effective and cost-effective treatment option with a novel mode of action. Furthermore, apremilast is an oral alternative to injectable biologic therapies, and does not require routine laboratory monitoring. This may result in reduced monitoring visits over time compared with biologic treatment, as noted by the clinical experts (ACD section 4.14). Patient choice is an important factor in shared decision making and may impact favourably on treatment outcomes in psoriasis.[i] Celgene agrees with the Appraisal Committee conclusion (ACD section 4.27) that patients with psoriasis value having a range of treatment options and that the use of apremilast would be largely driven by patient and physician choice.	Comments noted
British Association of Dermatologists	The British Association of Dermatologists welcomes the decision by NICE to recommend apremilast as an option for treating adults with severe chronic plaque psoriasis and circumstances indicated in the ACD.	Comments noted

Consultee	Comment	Response
The Psoriasis and Psoriatic Arthritis Alliance	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. As I recall from the data presented at the original appraisal meeting, apremilast was lesseffective when compared to biologic agents in those who might qualify. With a PAS, that benefit does not improve. I also note that the recommendation is now for severe psoriasis and not the fulla licence indication, which potentially limits the use of apremilast or may significantly increase its use in that group, given the potential acquisition cost saving. I fear that this may lead to those with the severest disease being offered a less effective treatment and therefore, not get optimal care. I do believe there is a place for an oral psoriasis therapy. I would like to see in 1.1 of the recommendation, clearer guidance where within the sequence of care apremilsat will be used, particularly when read in conjunction with other guidance for severe psoriasis, so that patients get appropriate access, and apremilast does not just displace or delay clinically more effective therapies in the severe psoriasis patient group.	Comments noted. See 1.1 and 4.32

Consultee	Comment	Response
The psoriasis Association	The Psoriasis Association welcomes the positive recommendation of apremilast as an option for people with severe chronic plaque psoriasis. 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 severe psoriasis who cannot or do not wish to use injected medications a new option. Additionally, apremilast has a different mode of action to any systemic or biologic medication which is currently available for psoriasis, meaning that it offers a genuine alternative for those who have not seen an acceptable response to other therapies. All of the above, along with the flexibility of apremilast's Marketing Authorisation allowing its use before, after, or instead of biologic therapies, mean that apremilast offers real treatment choice to patients and their healthcare professionals. I have read the Appraisal Confirmation 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 severe chronic plaque psoriasis.	Comments noted.

Comments received from commentators

Commentator	Comment [sic]	Response
Janssen	Thank you for the opportunity to comment on the above ACD. We have reviewed the details of the ACD and we would like to comment on the following points of the appraisal: **1. Lack of stopping rule** *Apremilast is recommended as an option for treating chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, for example, ciclosporin, methotrexate or PUVA (psoralen and ultraviolet-A light), or these treatments are contraindicated or the person cannot tolerate*	Comments noted See FAD sections 1.1 and 4.29

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<tr><th>Commentator</th><th>Comment [sic]</th><th>Response</th></tr>
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them, only when:

the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
the company provides apremilast with the discount agreed in the patient access scheme. [para 1.1]

Unlike the recommendations for biological therapies, the ACD recommendation for apremilast does not include a stopping rule. However, the apremilast cost-effectiveness model uses a trial period of 16 weeks for apremilast, ustekinumab and adalimumab, 12 weeks for etanercept and 10 weeks for infliximab; these numbers correspond to the NICE stopping rules of the comparators. Stopping rules ensure that patients have appropriately responded to the therapy and move to a different treatment if the patient response is suboptimal. Janssen considers the inclusion of a stopping rule appropriate for apremilast for the treatment of plaque psoriasis.
<u>Table 1.</u> NICE stopping rules and label recommendation in biologic treatment for plaque psoriasis
<table>
<tr><th>Treatment</th><th>Stopping rule per NICE guidance</th><th>Label – treatment discontinuation</th></tr>
<tr><td>Adalimumab (TA146)</td><td>16 weeks</td><td>16 weeks or dose frequency increase</td></tr>
<tr><td>Ustekinumab (TA180)</td><td>16 weeks</td><td>28 weeks</td></tr>
<tr><td>Etanercept (TA 103)</td><td>12 weeks</td><td>24 weeks</td></tr>
<tr><td>Secukinumab (TA 350)</td><td>12 weeks</td><td>None</td></tr>
<tr><td>Infliximab (TA 134)</td><td>10 weeks</td><td>14 weeks</td></tr>
<tr><td>Apremilast (ID987)</td><td>None (within in the current ACD)</td><td>28 weeks</td></tr>
</table>
</td><td></td></tr>
<tr><td>Janssen</td><td>
2. The cost of best supportive care
The committee discussed the sources used by the company to estimate resource use and costs associated with best supportive care. It noted that the incremental cost-effectiveness ratios (ICERs) were highly sensitive to these inputs, and specifically whether the model included hospitalisation rates and costs from Fonia et al. (2010; the ERG's preferred assumption of best supportive care costs of
</td><td>Comments noted, no changes to FAD required</td></tr>
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<tr><th>Commentator</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
£348 per cycle based on 6.49 days of hospitalisation per year) or NICE's psoriasis guideline (the company's base case assuming best supportive care costs £888 per cycle based on 26.6 days of hospitalisation per year).
[…]The committee noted that after consultation, the company provided NHS hospital episode statistics data that showed that the average length of hospital stay associated with best supportive care was 3.5 days. It heard from the company that in its view, these values underestimate actual length of NHS hospitalisation because they include people with different disease severities as well as people receiving concomitant medication and that, in patients who had received inpatient care, the average length of stay was 10.74 days. The clinical experts agreed that the hospital episode statistics
data underestimated length of hospitalisation. The committee agreed with this, but considered that the most plausible estimate would be lower than the ERG and company assumptions of 6.49 and 26.6 days per year [para 4.11].

Janssen believes that Fonia et al. 2010 may be an underestimate of the cost of best supportive care as it does not reflect the severity of the patients within the scope of this appraisal. To support this notion, we would like to highlight various sources of length of stay data in relation to severity of disease, based on treatment progression in Table 2 below. It is clear that the length of stay varies greatly depending upon where a patient lies within the treatment pathway. We will discuss each source of data in turn.

<u>Table 2.</u> Length of stay in relation to severity of disease based on treatment progression.
<table>
<tr><th>Topical therapy</th><th>Systemic therapy</th><th>1st biologics</th><th>2nd biologics</th><th>BSC</th><th>Reference</th><th>Source</th></tr>
<tr><td></td><td>6.49 days</td><td></td><td></td><td></td><td>Fonia et al (2010)</td><td>1</td></tr>
<tr><td></td><td></td><td></td><td></td><td>26.6 days</td><td>NICE CG153 (2012)</td><td>2</td></tr>
<tr><td colspan="5">16.8 days</td><td>Conway et al (2008)</td><td>3</td></tr>
<tr><td colspan="5">3.5 days</td><td>NHS statistics (recent 2014/2015)</td><td>4</td></tr>
<tr><td></td><td></td><td colspan="3">10.74 days</td><td>NHS statistics (severe) (recent 2014/2015)</td><td>5</td></tr>
</table>

During the Appraisal Committee meeting, the Committee referred to two potential sources of length of
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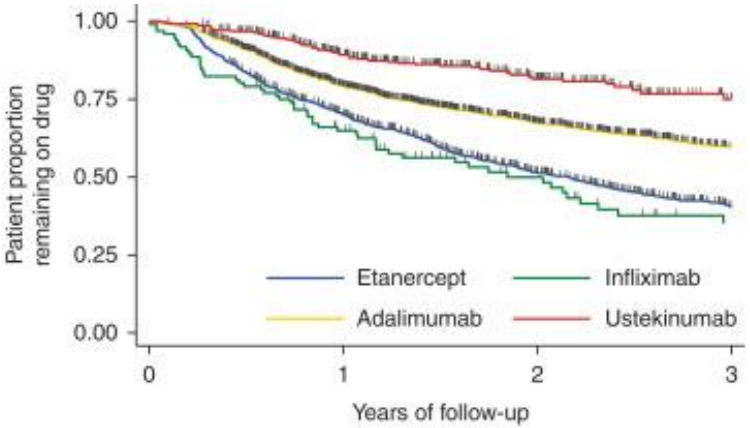
Commentator	Comment [sic]	Response
	stay data in relation to best supportive care –1) Fonia et al. 2010 and 2) the NICE CG153 (2012) for psoriasis. Fonia et al. 2010 collected retrospective data on hospital resource use and drug usage in the twelve months **before** initiation of biologic therapy and at least 6 months **after**; the value referred to in the appraisal (6.49 days) in fact corresponds to the group **before** initiation of biologic therapy (equating to systemic therapy in Table 2 and not to best supportive care). In contrast, NICE CG153 estimates the cost of best supportive care for people for patients that have failed two biologics or are intolerant/contraindicated to a biologic, which is clearly a more severe population compared to that studied in Fonia et al, 2010. This difference in the disease progression of these distinct patient populations is very likely the cause of the discrepancy between the £348 (based on a length of stay of 6.49 days) and the £888 (based on a length of stay of 26.6 days) per cycle in the economic model. In addition to these two sources of data identified during the appraisal, Janssen has identified another publication 3) Conway et al 2008) that found that the mean length of stay of patients with psoriasis in Wales was 16.8 days; this study reflects a mixed population from a disease severity perspective as it includes all patients hospitalised due to psoriasis. Lastly, also during the Appraisal Committee meeting, two alternative sources of length of stay data were identified from more recent NHS hospital episode statistics 4) 3.5 days for **all** psoriasis patients and 5) 10.74 days for patients **who had received inpatient care**. These figures again point to the difference in the length of stay based upon the severity of disease. The current apremilast submission uses a treatment sequencing model, where best supportive care can follow a sequence of one, two or three treatments. The greater the number of treatments a patient has failed, the more severe/refractory the patient is; however, the cost of BSC remains the same in all scenarios. Janssen does not believe this to be appropriate, as it is likely that more severe patients will incur increased costs as part of best supportive care. In summary, Janssen believes that Fonia reflects a less severe population than the population within the scope of this appraisal, and considers that a length of stay between 10.74 days to 26.6 days may be more reflective based on the severity of disease of the patients (Table 2).	
Janssen	**3. Withdrawal rates in the model** The third comment relates to the assumed withdrawal rates in the economic model. While it may be a necessary simplifying assumption to assume all therapies have the same withdrawal rate, this may not	Comments noted, no changes to FAD required

Commentator	Comment [sic]	Response
	be reflective of actual adherence rates observed in real-world practice. There is a growing body of evidence that suggests that adherence rates for biologics differ and some are higher than others. For example, recent BADBIR (British Association of Dermatologists Biologic Interventions Register) data, Warren et al. (2015), demonstrated that that in the UK, patients were more likely to persist on ustekinumab compared to infliximab, adalimumab, and etanercept (Figure 1). Janssen considers it important to consider the impact of different withdrawal rates by therapy, as measured in the literature, in the apremilast appraisal. **Figure 1. Crude drug survival of the first biologic course showing disaggregated biologic data (Kaplan–Meier survival curve). Warren et al. 2015**  Number at risk Etanercept 1,098 718 418 225 Infliximab 96 55 30 15 Adalimumab 1,879 1,175 596 277 Ustekinumab 450 307 120 40	
AbbVie	**Summary** As a commentator in relation to the above STA, we write in relation to the Appraisal Consultation Document (**ACD**) for Apremilast. On review of the ACD dated July 2016 for the treatment of moderate to severe plaque psoriasis, AbbVie has identified a number of issues which we believe have the potential to undermine the resulting guidance, and potentially the veracity of the NICE appraisal process. AbbVie's concerns fall into the following four broad categories which we address below:	Comments noted, no changes to FAD required.

Commentator	Comment [sic]	Response
	1. The ACD appears to have been developed contrary to the NICE Guide to the processes of technology appraisal dated September 2014 and the NICE Guide to methods of technology appraisal 2013; 2. There exists a lack of transparency in the ACD and supporting documentation; 3. Issues with the accuracy of quality and representativeness of clinical practice and technical implementation: and 4. The impact of NICE recommendations on people who currently receive Apremilast and who fall outside the NICE recommendations. Given the serious nature of these issues identified with the decision making process, we believe the company should be encouraged to re-submit an STA that addresses the scope, and/or the appraisal should be re-scoped as an MTA (including previous guidance). We sincerely encourage the Committee to reconsider its draft guidance in light of our detailed comments described below. <u>ii. Technical Implementation</u> In the executable model submitted by the company and made available to AbbVie, running the model with sequence A vs sequence B led to different costs than running the model with sequence B vs sequence A (despite the sequences being identical). We believe there may be an error of several hundred pounds in favour of sequence B. For consistency in decision making, the model should be demonstrated to be accurate by producing similar ICERs to those seen in previous appraisals (for example TA146) when given similar inputs. This has not been shown in the executable model, and our further analysis indicates it may not be the case.	
AbbVie	**Detailed comments** 1) <u>The guidance has not been developed in line with the NICE Methods and Process Guides</u> The rapid re-review process is intended to permit companies an opportunity to submit a patient access scheme ("PAS") to reduce their ICER, where an ICER has been agreed however is too high (e.g., the appraisal of eltrombopag for idiopathic thrombocytopenia). However in this appraisal the ACD lists a number of outstanding issues with both the clinical and economic evidence presented. These issues are discussed extensively in the ACD with the modelling only regarded as being *'generally sufficient'* (ACD Section 4.10), and the ERG stating: *"The ERG considered that the manufacturer's base-case cost-effectiveness results were not necessarily a sufficient basis to inform the most efficient use and position of apremilast"*. AbbVie supports both of these statements with additional concerns described below. The second area where we believe the NICE Methods Guide has not been followed is in the comparisons presented and on which a decision has been proposed. As such, this represents a risk of procedural impropriety. In the original company model, the choice presented was between two unrealistic sequences (in reality	Comments noted, no changes to FAD required. The uncertainty associated with the modelling was taken into account in the decision making

Commentator	Comment [sic]	Response
	no sequence will be followed by 100% of patients). This was paired back for decision making with an ICER presented only against best supportive care. To demonstrate cost effectiveness, a full incremental analysis should be conducted, as a drug may be cost-effective compared to one treatment, it may be a cost *ineffective* use of resources compared to the other treatments available on the market. We believe the company should not be permitted to submit irrelevant information, placing the committee in a position where a decision is made on irrelevant considerations. Should the submitting company wish to position the treatment before the use of biologic treatments, then a model comparing against the sequences used in clinical practice should have been presented (based on market share data), adequately adjusted for reductions in efficacy due to multiple lines of treatment and with projected treatment sequences included. Should the submitting company instead wish to compare against existing treatments and best supportive care, a full incremental analysis should be conducted. If this relevant information is submitted, we believe the cost effectiveness position could be substantially different.	
AbbVie	1) <u>The lack of transparency in the preliminary guidance</u> We draw your attention to section 3.1.24 of the NICE Process Guide which states that *"Confidential information in a submission should be kept to a minimum."*. Further, "Data that are likely to be fundamental to the Appraisal Committee's decision-making cannot be marked as confidential (for example, the list price of a technology after launch and incremental cost-effectiveness ratio [ICER] estimates". In these current circumstances the ACD and supporting documentation does not fit with the ethos of transparency in decision making by public bodies. We note that the company has censored all costs, QALYs, and ICERs. This makes it impossible for independent observers and members of the public to determine whether the NHS is in fact achieving value for money compared to existing therapies or to money spent elsewhere in the healthcare service. This transparency concern is compounded by the fact that apremilast is, based upon the evidence, therapeutically less effective than existing therapies. This point has been acknowledged by both the manufacturer and NICE stating: *"Response rates with apremilast (marked as 'academic in confidence' by the company) were lower than for the biological therapies; this difference was statistically significant for comparisons with all biological therapies except with etanercept."* – ACD from June 2015 page 10. Furthermore, the ERG noted that the PSOR-010 trial, which the submitting company used to support the above statement regarding etanercept, was not powered to compare etanercept and apremilast, therefore the statement regarding the response rates of apremilast compared with etanercept should be interpreted with caution. This lower efficacy, and decision (made in secret with no publicly available information on value for money), may lead parties to the reasonable conclusion that the NHS has chosen the 'cheaper' treatment, <u>*regardless of patient outcomes*</u>. AbbVie are unclear how the committee	Comments noted, see section 4.32 Due to the confidential status of the patient access scheme, the decision making ICERs cannot be released.

Commentator	Comment [sic]	Response
	has recommended a therapeutically less effective product on the basis of its lower price. This appears to us to be potentially irrational. Whilst we acknowledge the need for discretion regarding patient access schemes, the dual objectives of commercial confidentiality and transparent decision making must be achieved; for example the recent appraisals of trifluridine-tipiracel in previously treated metastatic colorectal cancer and nivolumab in combination with ipilimumab in advanced melanoma both had patient access schemes that cannot be back calculated, but allow the public to have faith in the decision making process which must not be undermined.	
AbbVie	3. Quality and representativeness of clinical practice and technical implementation In our capacity as a commentator, AbbVie has had full sight of the information presented by the company that we are entitled to have access to. However following our review of these documents, we have two main concerns regarding the accuracy of the economic modelling supporting the submission, namely (i) quality and representativeness of clinical practice, and (ii) technical implementation. i. Quality and representativeness of clinical practice The company's model assumes 100% of patients move from one treatment to the next. This is in the first instance highly unrealistic, and no data is presented on market shares of existing treatments to support this. The cost of "best supportive care" is a key driver of the model, as identified by the committee and ERG, with the potential to make treatments "highly cost-effective or cost-ineffective". Without further information on UK practice for the patients under consideration, it would appear false to assume the treatment is indeed cost-effective at all. We draw your attention to the Committee conclusion in the ACD at Section 4.11 which states, *"that the best supportive care costs are likely to be lower than in Fonia and also noted that assuming a lower cost would increase the ICER".*	Comments noted, see 4.14, 4.15
AbbVie	3. The impact of NICE recommendations on people who currently receive Apremilast and who fall outside the NICE recommendations. Apremilast is currently supplied by the marketing authorisation holder free of charge to patients whilst no routine funding on the NHS is available. Abbvie requests that NICE issue information clarifying that patients currently receiving apremilast through the free of charge scheme must fulfil the eligibility criteria as outlined in the ACD in order to continue access on the NHS. Those who fall outside the NICE recommendations must only remain on therapy whilst the marketing authorisation holder continues to supply apremilast free of charge. Should the availability of free of	Comments noted. This it outside of the remit of a technology appraisal.

Commentator	Comment [sic]	Response
	charge be withdrawn, these patients should be considered for alternative therapies. **Conclusion** In light of the seriousness of the matters we have identified with the ACD, we invite the committee to request a review of the submission, involving a major change in the recommendations, considerations and/or evidence base to be submitted by the company. In particular, the company should be encouraged to (i) re-submit an STA that addresses the requisite scope, and/or (ii) re-scope the appraisal as an MTA (including previous guidance). All submissions, decisions and relevant information to this STA process must as a minimum, be fair, transparent and justifiable to the public. The ACD as presented presently does not, in AbbVie's view, meet these requirements. We sincerely encourage the Committee to reconsider its draft guidance in light of our detailed comments. AbbVie Ltd **24 August 2016**	
MSD	MSD welcomes the opportunity to comment on the Appraisal Consultation Document for the assessment of apremilast for moderate to severe psoriasis. We would like to inform NICE that MSD has no comments on this Appraisal Consultation Document.	Comments noted.
Novartis	Thank you for your letter dated 27th July inviting comments 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. As requested, comments on the ACD are separated from those on the Committee Papers. <u>Has all of the relevant evidence been taken into account?</u> *Comment on the Committee Papers:* No. We are concerned that relevant evidence from the ERG has not been taken into account. In particular, on page 9 of the ERG review of the PAS submission of apremilast for the treatment of severe plaque psoriasis (page 99 of the Committee papers for ID987), there is a statement that *"the ERG believes that an error may have been made by the company when reporting the results. That is, the pre biologic positioning of apremilast has been incorrectly reported to dominate the post biologic positioning. The error appears to be in reporting of the incremental difference in QALYs i.e. the company incorrectly reporting this as a positive QALY difference in favour of the pre biologic positioning."* This may mean an	Comments noted. No changes required to the FAD

Commentator	Comment [sic]	Response
	erroneous conclusion has been drawn from the evidence supplied; instead of apremilast in the pre-biologic position dominating post-biologic usage, pre-biologic use may actually result in *fewer* QALYs.	
Novartis	*Comment on the ACD:* The impact of this potential misinterpretation by Celgene on the committee's recommendations is not discussed in the ACD, so we are unclear whether it has been considered by the committee.	Comment noted. The sequencing analyses were not used for decision making. See FAD section 4.30
Novartis	*Comment on the Committee Papers:* We agree with the ERG that Celgene's analyses "cannot be used to determine the optimal position of apremilast in clinical pathway".	Comment noted. No change to FAD required.
Novartis	*Comment on the ACD:* It is clear from the ACD that the committee's intention is aligned to clinical expert opinion (as outlined in paragraph 4.4 of the ACD) and is to "recommend apremilast as an option for treating severe chronic plaque psoriasis that has not responded to systemic therapy, or when systemic therapy is contraindicated or not tolerated" with positioning determined "largely by patient choice and by intolerance or contraindications (such as tuberculosis) to biological therapy" (see paragraph 4.27 of the ACD). Based on this intention, the current wording of the apremilast guidance raises two concerns: 1) Whilst the apremilast ACD states that apremilast is an option for "adults whose disease has not responded to other systemic therapies, for example, ciclosporin, methotrexate **or** PUVA", TA350 for secukinumab[1], TA180 for ustekinumab[2], TA146 for adalimumab[3] and TA103 for efalizumab and etanercept[4] all state that these therapies are options for patients when "the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate **and** PUVA". This difference in wording could be interpreted as positioning apremilast earlier in the treatment pathway than the biologic therapies (secukinumab and the TNFα inhibitors) i.e. after only one versus three systemic therapies. We understand this is not the committee's intention and request that the apremilast guidance wording be aligned to that of previous technology appraisal guidance in plaque psoriasis, to ensure that patient choice is respected in the manner that the committee intend.	Comment noted. Section 1.1 of FAD has been updated. The positioning of apremilast has been clarified in the FAD throughout. See sections 4.4-4.7 specifically
Novartis	2) The apremilast ACD does not contain any guidance on stopping criteria which we are concerned could lead to inappropriate long-term use of this less expensive and less effective therapy. This is despite the apremilast cost-effectiveness model containing a trial period for each treatment; an "initial 10 to 16 week period over which initial response to the treatment is assessed…at the end of the trial period,	Comment noted. See FAD section 4.29

Commentator	Comment [sic]	Response
	patients stay on that line of treatment if they have had a PASI improvement of 75% or more".[5] Guidance for the biologic therapies (secukinumab and the TNFα inhibitors) includes clear recommendations regarding treatment discontinuation in non-responders.[1-4] 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. We request that the committee considers the inclusion of appropriate stopping criteria, based on PASI 75 response, for patients who do not experience adequate clinical benefit with apremilast.	
Novartis	*Comment on the Committee Papers:* We would like to point out that paragraph 3.10 of Celgene's 3 Patient Access Scheme submission application form (details of the duration of the scheme) states that "The PAS will remain in place from the point of publication of a positive recommendation from NICE for the use of apremilast for the treatment of **moderate to** severe psoriasis [Rapid Review of TA368] until the recommendation is next reviewed by NICE and subject to the agreement of the DoH." The ACD recommendation only relates to patients with **severe** plaque psoriasis, so we query whether the PAS agreement requires revision to exclude reference to moderate psoriasis.	Comment noted. The appraisal considered moderate and severe psoriasis.
Novartis	*Comment on the ACD:* We believe there may be a typographical error at paragraph 4.22 of the ACD: "The committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as **not** an applicable consideration in its assessment of the cost effectiveness of branded medicines'." We believe the double-negative included in this sentence is unintentional and that it should instead read: "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".	Comment noted. Typo addressed
Novartis	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. Please see comments in response to the above question. Novartis agrees with the ERG that there are flaws in the clinical and cost effectiveness evidence presented by Celgene. In particular there is no basis to recommend apremilast as a treatment option before a biologic due to the limited clinical and cost effectiveness evidence to support use in this population. The EPAR for apremilast discusses the limitations of the clinical evidence base for	Comment noted. Section 1.1 of FAD has been updated. The positioning of apremilast has been clarified in the FAD throughout. See sections 4.4-4.7 specifically

Commentator	Comment [sic]	Response
	apremilast and states that "justification that the efficacy and safety data support a broad indication in patients in need of systemic therapy was considered inadequate"[6]. This contrasts with secukinumab where the EMA viewed the clinical evidence base as supportive of a broader indication, stating: "The study population included both systemic treatment naïve patients as well as those previously exposed to systemic therapies including biologic therapies…Therefore, the following indication is acceptable from the efficacy point of view: Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy".[7] Importantly the patient populations in the apremilast trials are not generalisable to the pre-biologic patient population since only 13% of PSO-008 trial population fit the criteria of prior systemic therapy without prior biologic therapy. Therefore, as outlined in our response to the previous question, we request the committee review the current apremilast guidance wording to ensure that it cannot be interpreted as a recommendation for long-term use of apremilast pre-biologics, which would be contrary to the committee's intent and the clinical expert opinion outlined in paragraph 4.4 of the ACD: "in general, apremilast would not displace a biological therapy in the treatment pathway" and "the positioning of apremilast (either before or after biological therapy) would be driven largely by patient choice and intolerance or contraindications to biological therapy such as serious infections". Biologic therapy is a more effective treatment option for people with plaque psoriasis (PASI 75 across biologic trials in the range of 75.9 to 86.7%[1]; compared with 29 -33% for apremilast[8]), and has been accepted as a cost-effective use of NHS resources[1-4], so for psoriasis patients who prefer biologic therapy based on greater efficacy or a different safety profile, it should be made available.	
Novartis	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 severe, chronic plaque psoriasis may be interpreted as a pre-biologic recommendation, which would be inappropriate based on the committee's interpretation of the evidence. In addition, if there has been a misinterpretation of the cost-effectiveness analysis comparing use of apremilast pre- versus post-biologics, we are concerned that the current provisional recommendation could result in an inefficient allocation of scarce NHS resources towards a less effective therapy. We request that the committee reviews the apremilast guidance wording to ensure it is aligned with that of biologic therapy, and cannot be interpreted as a recommendation for long-term use of apremilast earlier in the treatment pathway than the biologic options.	Comment noted. Section 1.1 of FAD has been updated. The positioning of apremilast has been clarified in the FAD throughout. See sections 4.4-4.7 specifically.
Novartis	Are there any aspects of the recommendations that need particular consideration to ensure we avoid	Comment noted

Commentator	Comment [sic]	Response
	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	
Pfizer	No comments	Comment noted

[i] Umar N, Yamamoto S, Loerbroks A, Terris D. Elicitation and use of patients' preferences in the treatment of psoriasis: a systematic review. *Acta Derm Venereol* 2012;92:341-6.

Celgene welcomes the draft positive recommendation for apremilast in moderate to severe chronic plaque psoriasis and considers that apremilast would represent a valuable addition to the current range of treatment options available to patients in England and Wales.

Severe psoriasis is a multi-faceted condition with a significant psychosocial impact which substantially decreases quality of life. The optimal treatment strategy in psoriasis is dependent on multiple factors and can be highly individualized based on individual patient needs.

Apremilast offers an additional, clinically effective and cost-effective treatment option with a novel mode of action. Furthermore, apremilast is an oral alternative to injectable biologic therapies, and does not require routine laboratory monitoring. This may result in reduced monitoring visits over time compared with biologic treatment, as noted by the clinical experts (ACD section 4.14).

Patient choice is an important factor in shared decision making and may impact favourably on treatment outcomes in psoriasis.[i] Celgene agrees with the Appraisal Committee conclusion (ACD section 4.27) that patients with psoriasis value having a range of treatment options and that the use of apremilast would be largely driven by patient and physician choice.

References

[i] Umar N, Yamamoto S, Loerbroks A, Terris D. Elicitation and use of patients' preferences in the treatment of psoriasis: a systematic review. *Acta Derm Venereol* 2012;92:341-6.

8th August 2016

Apremilast for treating moderate to severe plaque psoriasis: Appraisal Consultation Document

To whom it may concern,

The Psoriasis Association welcomes the positive recommendation of apremilast as an option for people with severe chronic plaque psoriasis.

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 severe psoriasis who cannot or do not wish to use injected medications a new option. Additionally, apremilast has a different mode of action to any systemic or biologic medication which is currently available for psoriasis, meaning that it offers a genuine alternative for those who have not seen an acceptable response to other therapies. All of the above, along with the flexibility of apremilast's Marketing Authorisation allowing its use before, after, or instead of biologic therapies, mean that apremilast offers real treatment choice to patients and their healthcare professionals.

I have read the Appraisal Confirmation 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 severe chronic plaque psoriasis.

Yours faithfully,

[redacted]

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24 August 2016

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Dear Meindert

Apremilast moderate to severe - psoriasis
(rapid review of TA368)

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.

As I recall from the data presented at the original appraisal meeting, apremilast was less-effective when compared to biologic agents in those who might qualify. With a PAS, that benefit does not improve. I also note that the recommendation is now for severe psoriasis and not the full licence indication, which potentially limits the use of apremilast or may significantly increase its use in that group, given the potential acquisition cost saving. I fear that this may lead to those with the severest disease being offered a less effective treatment and therefore, not get optimal care.

I do believe there is a place for an oral psoriasis therapy. I would like to see in 1.1 of the recommendation, clearer guidance where within the sequence of care apremilsat will be used, particularly when read in conjunction with other guidance for severe psoriasis, so that patients get appropriate access, and apremilast does not just displace or delay clinically more effective therapies in the severe psoriasis patient group.

Yours sincerely

[redacted]

British Association of Dermatologists
Response to NICE Appraisal Consultation Document
on the Single Technology Appraisal (rapid review)
Apremilast moderate to severe - psoriasis (rapid review of TA368) [ID987]
August 2016

The British Association of Dermatologists welcomes the decision by NICE to recommend apremilast as an option for treating adults with severe chronic plaque psoriasis and circumstances indicated in the ACD.

AbbVie comments on the Appraisal Consultation Document for Apremilast (Otezla) for the treatment of moderate to severe plaque psoriasis

Summary

As a commentator in relation to the above STA, we write in relation to the Appraisal Consultation Document (**ACD**) for Apremilast. On review of the ACD dated July 2016 for the treatment of moderate to severe plaque psoriasis, AbbVie has identified a number of issues which we believe have the potential to undermine the resulting guidance, and potentially the veracity of the NICE appraisal process.

AbbVie's concerns fall into the following four broad categories which we address below:

1. The ACD appears to have been developed contrary to the NICE Guide to the processes of technology appraisal dated September 2014 and the NICE Guide to methods of technology appraisal 2013;
2. There exists a lack of transparency in the ACD and supporting documentation;
3. Issues with the accuracy of quality and representativeness of clinical practice and technical implementation: and
4. The impact of NICE recommendations on people who currently receive Apremilast and who fall outside the NICE recommendations.

Given the serious nature of these issues identified with the decision making process, we believe the company should be encouraged to re-submit an STA that addresses the scope, and/or the appraisal should be re-scoped as an MTA (including previous guidance). We sincerely encourage the Committee to reconsider its draft guidance in light of our detailed comments described below.

Detailed comments

1) <u>The guidance has not been developed in line with the NICE Methods and Process Guides</u>

The rapid re-review process is intended to permit companies an opportunity to submit a patient access scheme ("PAS") to reduce their ICER, where an ICER has been agreed however is too high (e.g., the appraisal of eltrombopag for idiopathic thrombocytopenia). However in this appraisal the ACD lists a number of outstanding issues with both the clinical and economic evidence presented. These issues are discussed extensively in the ACD with the modelling only regarded as being *'generally sufficient'* (ACD Section 4.10), and the ERG stating:

> *"The ERG considered that the manufacturer's base-case cost-effectiveness results were not necessarily a sufficient basis to inform the most efficient use and position of apremilast"*.

AbbVie supports both of these statements with additional concerns described below.

The second area where we believe the NICE Methods Guide has not been followed is in the comparisons presented and on which a decision has been proposed. As such, this represents a risk of procedural impropriety.

In the original company model, the choice presented was between two unrealistic sequences (in reality no sequence will be followed by 100% of patients). This was paired back for decision making

with an ICER presented only against best supportive care. To demonstrate cost effectiveness, a full incremental analysis should be conducted, as a drug may be cost-effective compared to one treatment, it may be a cost *ineffective* use of resources compared to the other treatments available on the market. We believe the company should not be permitted to submit irrelevant information, placing the committee in a position where a decision is made on irrelevant considerations.

Should the submitting company wish to position the treatment before the use of biologic treatments, then a model comparing against the sequences used in clinical practice should have been presented (based on market share data), adequately adjusted for reductions in efficacy due to multiple lines of treatment and with projected treatment sequences included. Should the submitting company instead wish to compare against existing treatments and best supportive care, a full incremental analysis should be conducted. If this relevant information is submitted, we believe the cost effectiveness position could be substantially different.

2) <u>The lack of transparency in the preliminary guidance</u>

We draw your attention to section 3.1.24 of the NICE Process Guide which states that *"Confidential information in a submission should be kept to a minimum."*. Further, "Data that are likely to be fundamental to the Appraisal Committee's decision-making cannot be marked as confidential (for example, the list price of a technology after launch and incremental cost-effectiveness ratio [ICER] estimates".

In these current circumstances the ACD and supporting documentation does not fit with the ethos of transparency in decision making by public bodies. We note that the company has censored all costs, QALYs, and ICERs. This makes it impossible for independent observers and members of the public to determine whether the NHS is in fact achieving value for money compared to existing therapies or to money spent elsewhere in the healthcare service.

This transparency concern is compounded by the fact that apremilast is, based upon the evidence, therapeutically less effective than existing therapies. This point has been acknowledged by both the manufacturer and NICE stating:

> *"Response rates with apremilast (marked as 'academic in confidence' by the company) were lower than for the biological therapies; this difference was statistically significant for comparisons with all biological therapies except with etanercept."* – ACD from June 2015 page 10.

Furthermore, the ERG noted that the PSOR-010 trial, which the submitting company used to support the above statement regarding etanercept, was not powered to compare etanercept and apremilast, therefore the statement regarding the response rates of apremilast compared with etanercept should be interpreted with caution. This lower efficacy, and decision (made in secret with no publicly available information on value for money), may lead parties to the reasonable conclusion that the NHS has chosen the 'cheaper' treatment, <u>*regardless of patient outcomes*</u>. AbbVie are unclear how the committee has recommended a therapeutically less effective product on the basis of its lower price. This appears to us to be potentially irrational.

Whilst we acknowledge the need for discretion regarding patient access schemes, the dual objectives of commercial confidentiality and transparent decision making must be achieved; for example the recent appraisals of trifluridine-tipiracel in previously treated metastatic colorectal cancer and nivolumab in combination with ipilimumab in advanced melanoma both had patient access schemes that cannot be back calculated, but allow the public to have faith in the decision making process which must not be undermined.

3. Quality and representativeness of clinical practice and technical implementation

In our capacity as a commentator, AbbVie has had full sight of the information presented by the company that we are entitled to have access to. However following our review of these documents, we have two main concerns regarding the accuracy of the economic modelling supporting the submission, namely (i) quality and representativeness of clinical practice, and (ii) technical implementation.

i. Quality and representativeness of clinical practice

The company's model assumes 100% of patients move from one treatment to the next. This is in the first instance highly unrealistic, and no data is presented on market shares of existing treatments to support this.

The cost of "best supportive care" is a key driver of the model, as identified by the committee and ERG, with the potential to make treatments "highly cost-effective or cost-ineffective". Without further information on UK practice for the patients under consideration, it would appear false to assume the treatment is indeed cost-effective at all. We draw your attention to the Committee conclusion in the ACD at Section 4.11 which states,

> *"that the best supportive care costs are likely to be lower than in Fonia and also noted that assuming a lower cost would increase the ICER".*

ii. Technical Implementation

In the executable model submitted by the company and made available to AbbVie, running the model with sequence A vs sequence B led to different costs than running the model with sequence B vs sequence A (despite the sequences being identical). We believe there may be an error of several hundred pounds in favour of sequence B.

For consistency in decision making, the model should be demonstrated to be accurate by producing similar ICERs to those seen in previous appraisals (for example TA146) when given similar inputs. This has not been shown in the executable model, and our further analysis indicates it may not be the case.

4. The impact of NICE recommendations on people who currently receive Apremilast and who fall outside the NICE recommendations.

Apremilast is currently supplied by the marketing authorisation holder free of charge to patients whilst no routine funding on the NHS is available. Abbvie requests that NICE issue information clarifying that patients currently receiving apremilast through the free of charge scheme must fulfil the eligibility criteria as outlined in the ACD in order to continue access on the NHS.

Those who fall outside the NICE recommendations must only remain on therapy whilst the marketing authorisation holder continues to supply apremilast free of charge. Should the availability of free of charge be withdrawn, these patients should be considered for alternative therapies.

Conclusion

In light of the seriousness of the matters we have identified with the ACD, we invite the committee to request a review of the submission, involving a major change in the recommendations, considerations and/or evidence base to be submitted by the company.

In particular, the company should be encouraged to (i) re-submit an STA that addresses the requisite scope, and/or (ii) re-scope the appraisal as an MTA (including previous guidance).

All submissions, decisions and relevant information to this STA process must as a minimum, be fair, transparent and justifiable to the public. The ACD as presented presently does not, in AbbVie's view, meet these requirements.

We sincerely encourage the Committee to reconsider its draft guidance in light of our detailed comments.

AbbVie Ltd

24 August 2016

Response to the First Appraisal Consultation Document (ACD) Apremilast for treating severe plaque psoriasis [ID987]

22nd August 2016

Thank you for the opportunity to comment on the above ACD. We have reviewed the details of the ACD and we would like to comment on the following points of the appraisal:

1. Lack of stopping rule

Apremilast is recommended as an option for treating chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, for example, ciclosporin, methotrexate or PUVA (psoralen and ultraviolet-A light), or these treatments are contraindicated or the person cannot tolerate them, only when:

- *the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10*
- *the company provides apremilast with the discount agreed in the patient access scheme. [para 1.1]*

Unlike the recommendations for biological therapies, the ACD recommendation for apremilast does not include a stopping rule. However, the apremilast cost-effectiveness model uses a trial period of 16 weeks for apremilast, ustekinumab and adalimumab, 12 weeks for etanercept and 10 weeks for infliximab; these numbers correspond to the NICE stopping rules of the comparators. Stopping rules ensure that patients have appropriately responded to the therapy and move to a different treatment if the patient response is suboptimal. Janssen considers the inclusion of a stopping rule appropriate for apremilast for the treatment of plaque psoriasis.

Table 1. NICE stopping rules and label recommendation in biologic treatment for plaque psoriasis

Treatment	Stopping rule per NICE guidance	Label – treatment discontinuation
Adalimumab (TA146)	16 weeks	16 weeks or dose frequency increase
Ustekinumab (TA180)	16 weeks	28 weeks
Etanercept (TA 103)	12 weeks	24 weeks
Secukinumab (TA 350)	12 weeks	None
Infliximab (TA 134)	10 weeks	14 weeks
Apremilast (ID987)	None (within in the current ACD)	28 weeks

2. The cost of best supportive care

The committee discussed the sources used by the company to estimate resource use and costs associated with best supportive care. It noted that the incremental cost-effectiveness ratios (ICERs) were highly sensitive to these inputs, and specifically whether the model included hospitalisation rates and costs from Fonia et al. (2010; the ERG's preferred assumption of best supportive care costs of £348 per cycle based on 6.49 days of hospitalisation per year) or NICE's psoriasis guideline (the company's base case assuming best supportive care costs £888 per cycle based on 26.6 days of hospitalisation per year).
[…]The committee noted that after consultation, the company provided NHS hospital episode statistics data that showed that the average length of hospital stay associated with best supportive care was 3.5 days. It heard from the company that in its view, these values underestimate actual length of NHS hospitalisation because they include people with different disease severities as well as people receiving concomitant medication and that, in patients who had received inpatient care, the average length of stay was 10.74 days. The clinical experts agreed that the hospital episode statistics data underestimated length of hospitalisation. The committee agreed with this, but considered that the most plausible estimate would be lower than the ERG and company assumptions of 6.49 and 26.6 days per year [para 4.11].

Janssen believes that Fonia et al. 2010 may be an underestimate of the cost of best supportive care as it does not reflect the severity of the patients within the scope of this appraisal. To support this notion, we would like to highlight various sources of length of stay data in relation to severity of disease, based on treatment progression in Table 2 below. It is clear that the length of stay varies greatly depending upon where a patient lies within the treatment pathway. We will discuss each source of data in turn.

Table 2. Length of stay in relation to severity of disease based on treatment progression.

Topical therapy	Systemic therapy	1st biologics	2nd biologics	BSC	Reference	Source
	6.49 days				Fonia et al (2010)	1
				26.6 days	NICE CG153 (2012)	2
16.8 days					Conway et al (2008)	3
3.5 days					NHS statistics (recent 2014/2015)	4
		10.74 days			NHS statistics (severe) (recent 2014/2015)	5

During the Appraisal Committee meeting, the Committee referred to two potential sources of length of stay data in relation to best supportive care –1) Fonia et al. 2010 and 2) the NICE CG153 (2012) for psoriasis. Fonia et al. 2010 collected retrospective data on hospital resource use and drug usage in the twelve months **before** initiation of biologic therapy and at least 6 months **after**; the value referred to in the appraisal (6.49 days) in fact corresponds to the group **before** initiation of biologic therapy (equating to systemic therapy in Table 2 and not to best supportive care). In contrast, NICE CG153 estimates the cost of best supportive care for people for patients that have failed two biologics or are intolerant/contraindicated to a biologic, which is clearly a more severe population compared to that studied in Fonia et al, 2010. This difference in the disease progression of these distinct patient populations is very likely the cause of the discrepancy between the £348 (based on a

length of stay of 6.49 days) and the £888 (based on a length of stay of 26.6 days) per cycle in the economic model.

In addition to these two sources of data identified during the appraisal, Janssen has identified another publication 3) Conway et al 2008) that found that the mean length of stay of patients with psoriasis in Wales was 16.8 days; this study reflects a mixed population from a disease severity perspective as it includes all patients hospitalised due to psoriasis.

Lastly, also during the Appraisal Committee meeting, two alternative sources of length of stay data were identified from more recent NHS hospital episode statistics 4) 3.5 days for **all** psoriasis patients and 5) 10.74 days for patients **who had received inpatient care**. These figures again point to the difference in the length of stay based upon the severity of disease.

The current apremilast submission uses a treatment sequencing model, where best supportive care can follow a sequence of one, two or three treatments. The greater the number of treatments a patient has failed, the more severe/refractory the patient is; however, the cost of BSC remains the same in all scenarios. Janssen does not believe this to be appropriate, as it is likely that more severe patients will incur increased costs as part of best supportive care.

In summary, Janssen believes that Fonia reflects a less severe population than the population within the scope of this appraisal, and considers that a length of stay between 10.74 days to 26.6 days may be more reflective based on the severity of disease of the patients (Table 2).

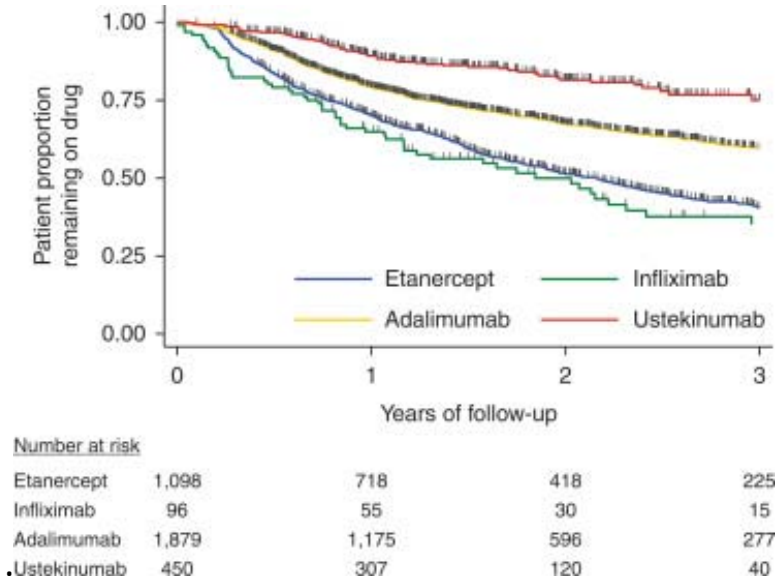
3. Withdrawal rates in the model

The third comment relates to the assumed withdrawal rates in the economic model. While it may be a necessary simplifying assumption to assume all therapies have the same withdrawal rate, this may not be reflective of actual adherence rates observed in real-world practice.

There is a growing body of evidence that suggests that adherence rates for biologics differ and some are higher than others. For example, recent BADBIR (British Association of Dermatologists Biologic Interventions Register) data, Warren et al. (2015), demonstrated that that in the UK, patients were more likely to persist on ustekinumab compared to infliximab, adalimumab, and etanercept (Figure 1).

Janssen considers it important to consider the impact of different withdrawal rates by therapy, as measured in the literature, in the apremilast appraisal.

Figure 1. Crude drug survival of the first biologic course showing disaggregated biologic data (Kaplan–Meier survival curve). Warren et al. 2015



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4. NICE TA350 Secukinumab for treating moderate to severe plaque psoriasis https://www.nice.org.uk/guidance/ta350
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12th August 2016

Dear [redacted]

RE: APREMILAST MODERATE TO SEVERE - PSORIASIS (RAPID REVIEW OF TA368) [ID987]

MSD welcomes the opportunity to comment on the Appraisal Consultation Document for the assessment of apremilast for moderate to severe psoriasis.

We would like to inform NICE that MSD has no comments on this Appraisal Consultation Document.

Please do not hesitate to contact us if you have any further requests or questions.

Kind regards,

[redacted]

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24th August 2016

Dear [redacted]

Re: Apremilast moderate to severe - psoriasis (rapid review of TA368) [ID987] – Appraisal Consultation Document

Thank you for your letter dated 27th July inviting comments 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. As requested, comments on the ACD are separated from those on the Committee Papers.

Has all of the relevant evidence been taken into account?

Comment on the Committee Papers:

No. We are concerned that relevant evidence from the ERG has not been taken into account. In particular, on page 9 of the ERG review of the PAS submission of apremilast for the treatment of severe plaque psoriasis (page 99 of the Committee papers for ID987), there is a statement that *"the ERG believes that an error may have been made by the company when reporting the results. That is, the pre biologic positioning of apremilast has been incorrectly reported to dominate the post biologic positioning. The error appears to be in reporting of the incremental difference in QALYs i.e. the company incorrectly reporting this as a positive QALY difference in favour of the pre biologic positioning."* This may mean an erroneous conclusion has been drawn from the evidence supplied; instead of apremilast in the pre-biologic position dominating post-biologic usage, pre-biologic use may actually result in *fewer* QALYs.

Comment on the ACD:

The impact of this potential misinterpretation by Celgene on the committee's recommendations is not discussed in the ACD, so we are unclear whether it has been considered by the committee.

Comment on the Committee Papers:

We agree with the ERG that Celgene's analyses "cannot be used to determine the optimal position of apremilast in clinical pathway".

Comment on the ACD:

It is clear from the ACD that the committee's intention is aligned to clinical expert opinion (as outlined in paragraph 4.4 of the ACD) and is to "recommend apremilast as an option for treating severe chronic plaque psoriasis that has not responded to systemic therapy, or when systemic therapy is contraindicated or not tolerated" with positioning determined "largely by patient choice and by intolerance or contraindications (such as tuberculosis) to biological therapy" (see paragraph 4.27 of the ACD).

Based on this intention, the current wording of the apremilast guidance raises two concerns:

1) Whilst the apremilast ACD states that apremilast is an option for "adults whose disease has not responded to other systemic therapies, for example, ciclosporin, methotrexate **or** PUVA", TA350 for secukinumab[1], TA180 for ustekinumab[2], TA146 for adalimumab[3] and TA103 for efalizumab and etanercept[4] all state that these therapies are options for patients when "the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate **and** PUVA".

This difference in wording could be interpreted as positioning apremilast earlier in the treatment pathway than the biologic therapies (secukinumab and the TNFα inhibitors) i.e. after only one versus three systemic therapies. We understand this is not the committee's intention and request that the apremilast guidance wording be aligned to that of previous technology appraisal guidance in plaque psoriasis, to ensure that patient choice is respected in the manner that the committee intend.

2) The apremilast ACD does not contain any guidance on stopping criteria which we are concerned could lead to inappropriate long-term use of this less expensive and less effective therapy. This is despite the apremilast cost-effectiveness model containing a trial period for each treatment; an "initial 10 to 16 week period over which initial response to the treatment is assessed…at the end of the trial period, patients stay on that line of treatment if they have had a PASI improvement of 75% or more".[5] Guidance for the biologic therapies (secukinumab and the TNFα inhibitors) includes clear recommendations regarding treatment discontinuation in non-responders.[1-4] 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. We request that the committee considers the inclusion of appropriate stopping criteria, based on PASI 75 response, for patients who do not experience adequate clinical benefit with apremilast.

Comment on the Committee Papers:

We would like to point out that paragraph 3.10 of Celgene's 3 Patient Access Scheme submission application form (details of the duration of the scheme) states that "The PAS will remain in place from the point of publication of a positive recommendation from NICE for the use of apremilast for the treatment of **moderate to** severe psoriasis [Rapid Review of TA368] until the recommendation is next reviewed by NICE and subject to the agreement of the DoH." The ACD recommendation only relates to patients with **severe** plaque psoriasis, so we query whether the PAS agreement requires revision to exclude reference to moderate psoriasis.

Comment on the ACD:

We believe there may be a typographical error at paragraph 4.22 of the ACD: "The committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as **not** an applicable consideration in its assessment of the cost effectiveness of branded medicines'." We believe the double-negative included in this sentence is unintentional and that it should instead read: "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".

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

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

Novartis agrees with the ERG that there are flaws in the clinical and cost effectiveness evidence presented by Celgene. In particular there is no basis to recommend apremilast as a treatment option before a biologic due to the limited clinical and cost effectiveness evidence to support use in this population. The EPAR for apremilast discusses the limitations of the clinical evidence base for apremilast and states that "justification that the efficacy and safety data support a broad indication in patients in need of systemic therapy was considered inadequate"[6]. This contrasts with secukinumab where the EMA viewed the clinical evidence base as supportive of a broader indication, stating: "The study population included both systemic treatment naïve patients as well as those previously exposed to systemic therapies including biologic therapies…Therefore, the following indication is acceptable from the efficacy point of view: Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy".[7] Importantly the patient populations in the apremilast trials are not generalisable to the pre-biologic patient population since only 13% of PSO-008 trial population fit the criteria of prior systemic therapy without prior biologic therapy.

Therefore, as outlined in our response to the previous question, we request the committee review the current apremilast guidance wording to ensure that it cannot be interpreted as a recommendation for long-term use of apremilast pre-biologics, which would be contrary to the committee's intent and the clinical expert opinion outlined in paragraph 4.4 of the ACD: "in general, apremilast would not displace a biological therapy in the treatment pathway" and

"the positioning of apremilast (either before or after biological therapy) would be driven largely by patient choice and intolerance or contraindications to biological therapy such as serious infections". Biologic therapy is a more effective treatment option for people with plaque psoriasis (PASI 75 across biologic trials in the range of 75.9 to 86.7%[1]; compared with 29 -33% for apremilast[8]), and has been accepted as a cost-effective use of NHS resources[1-4], so for psoriasis patients who prefer biologic therapy based on greater efficacy or a different safety profile, it should be made available.

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 severe, chronic plaque psoriasis may be interpreted as a pre-biologic recommendation, which would be inappropriate based on the committee's interpretation of the evidence.

In addition, if there has been a misinterpretation of the cost-effectiveness analysis comparing use of apremilast pre- versus post-biologics, we are concerned that the current provisional recommendation could result in an inefficient allocation of scarce NHS resources towards a less effective therapy.

We request that the committee reviews the apremilast guidance wording to ensure it is aligned with that of biologic therapy, and cannot be interpreted as a recommendation for long-term use of apremilast earlier in the treatment pathway than the biologic options.

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.

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 [TA350]. Secukinumab for treating moderate to severe plaque psoriasis. July 2015.

2. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA180]. Ustekinumab for the treatment of adults with moderate to severe psoriasis. September 2009.
3. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA146]. Adalimumab for the treatment of adults with psoriasis. June 2008.
4. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA103]. Etanercept and efalizumab for the treatment of adults with psoriasis. July 2006.
5. Evidence Review Group Report – Apremilast for treating moderate to severe plaque psoriasis. CRD/CHE University of York, Wade et al. 10th March 2015.
6. European Medicines Agency (EMA). Otezla : EPAR - Public Assessment Report. [EMA/CHMP/476353/2014]. 20 November 2014
7. European Medicines Agency (EMA). Cosentyx : EPAR - Public Assessment Report. [EMA/CHMP/389874/2014]. 20 November 2014
8. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA368]. Apremilast for treating moderate to severe plaque psoriasis. November 2015.

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

Name	[redacted]
Role	[redacted]
Other role	Consultant Dermatologist
Organisation	
Location	England
Conflict	Yes
Notes	My department has in the past been involved in phase 3 clinical research around this medication (a national study where my Trust was one of a few centres, and I was the PI at my centre). I am not currently involved in any research around this product.

Comments on individual sections of the ACD:

I am a Consultant Dermatologist at Barts Health (Whipps Cross University hospital and the Royal London Hospital). I am responsible for the management of many patients who have moderate to severe psoriasis who may require treatment with biologics or biologic equivalents at my Trust. I have had direct experience of using apremilast in clinical trials for several of my patients with moderate to severe psoriasis.

I welcome the draft positive recommendation for apremilast, a significant step forward in patient choice. Apremilast is an oral alternative to injectable biologics when patients have failed systemic conventional and biologics medication, and has a specific and different method of activity compared to other systemic and biologic alternatives The safety profile of apremilast appears from current studies, to be favourable especially when compared to those associated with many injectable biologics (and some systemics). The fact that apremilast is an oral preparation is useful for many patients in terms of their adherence to medication, and for those patients who are needle phobic. Apremilast seems to require much less blood monitoring and there may be therefore less of a burden in terms of follow up for healthcare professionals. Many of my patients who have scalp, nail and genital psoriasis as well as generalised disease have been successfully treated with apremilast and have responded to treatment in all affected areas. It is for these reasons that it is important that patients with moderate to severe psoriasis who have failed conventional systemic or biologic treatments in the UK have access to this important newer treatment