NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people [ID854]

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:
   - Abbvie
   - Janssen
   - Psoriasis Association
   - Psoriasis and Psoriatic Arthritis Alliance
   - British Association of Dermatologists
   - Royal College of Pathologists

3. **Addendum prepared by the Assessment Group**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people

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
AbbVie	AbbVie welcomes the opportunity to comment on the appraisal consultation document by the NICE Appraisal Committee for the ongoing multiple technology appraisal of adalimumab, etanercept and ustekinumab in psoriasis (plaque, chronic, severe, children, young people). Please find our comments summarised below:	Thank you for your response.
AbbVie	**1) Has all the relevant evidence been taken into account?** Yes, AbbVie believes that all relevant evidence has been taken into account by the Appraisal Committee in drafting the Appraisal Consultation Document (ACD).	Comment noted.
AbbVie	**2) Are the summaries of clinical and cost-effectiveness evidence reasonable interpretation of the evidence?** Yes, AbbVie believes that the summaries of both clinical and cost-effectiveness evidence included in the ACD are a reasonable interpretation of the evidence	Comment noted.
AbbVie	**3) Are the recommendations sound and a suitable basis for guidance to the NHS?** Yes, AbbVie believes that the recommendations are sound and a suitable basis for guidance to the NHS.	Comment noted.

Consultee	Comment [sic]	Response
AbbVie	**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?** No, AbbVie does not think there are any aspects of the recommendations that need particular considerations with respect to the factors listed at point 4).	Comment noted.
AbbVie	**5) Other comments:** The wording used in Section 2 of the ACD, page 5, in correspondence to "Prices", should be changed to accurately reflect the SmPC for adalimumab, so to include the words herewith highlighted " [..] or vial for paediatric use", as follows: "[..] The list prices (excluding VAT; 'British national formulary' [BNF] online, March 2017) are: £352.14 for 40 mg adalimumab in a prefilled pen or prefilled syringe or vial for paediatric use".	Comment noted. Section 2 has been amended. Please see the final appraisal determination (FAD).

Consultee	Comment [sic]	Response
Janssen	Janssen welcomes the opportunity to comment on the NICE appraisal consultation document (ACD) for the review of plaque psoriasis in children and young people – adalimumab, etanercept and ustekinumab [ID854]. We welcome the initial positive recommendation for the use of adalimumab, etanercept and ustekinumab for children and young people with severe psoriasis. We agree with the appraisal committee that psoriasis in children and young people significantly impacts their quality of life and can lead to psychosocial problems in their most formative years. We also welcome the committee's overall positive recommendations regarding biologics and their important role in treating severe psoriasis when standard systemic therapies (such as ciclosporin, methotrexate or phototherapy) have failed. However, we do continue to have concerns regarding some of the economic evidence conclusions in the ACD. Overall, we suggest the following key points should be considered further by the appraisal committee:	Thank you for your response. Please see the responses to each issue below.
Janssen	**1. Ustekinumab being recommended after the use of etanercept and adalimumab despite the appraisal committee's conclusion that ustekinumab is a more effective treatment option than etanercept. This continues to cause equity concerns regarding access to biologics in children and young people (below 18 years) when compared to adults.** 1.1 Both the network meta-analysis and clinical expert opinion suggested that etanercept is less effective than adalimumab and ustekinumab. We are concerned that both patients and clinicians will not have the option to use ustekinumab despite it being an effective treatment option. Furthermore, this continues to highlight an equity concern regarding equal access to biologics between children and adult with severe psoriasis, as adults will have the option to use ustekinumab as a first line biologic option but children and young people will be denied access. *The consultee submitted further information and references about this comment in its response to consultation. These have not been reproduced here. Please see Committee papers for the full response.*	After considering the comments received in response to the appraisal consultation document, the committee recommended adalimumab, etanercept and ustekinumab. Please see sections 1 and 4.22 of the final appraisal determination (FAD) for the committee's recommendations and full considerations.

Consultee	Comment [sic]	Response
Janssen	**2. Inconsistency in the appraisal committee's interpretation of the economic incremental analysis regarding etanercept and ustekinumab.** 2.1 There appears to be an inconsistent interpretation of the cost effectiveness decision rules in the ACD, specifically including etanercept which is extendedly dominated by adalimumab, but has been recommended as a cost-effective first line biologic treatment option in patients aged 12 and above (population 3). Yet, ustekinumab which currently has an ICER above £30,000 per QALY compared to adalimumab in the incremental analysis has not been recommended as a first line biologic. In our view, all three biologics represent a costeffective option compared to BSC if a pairwise analysis is undertaken rather than an incremental analysis. *The consultee submitted further information and references about this comment in its response to consultation. These have not been reproduced here. Please see Committee papers for the full response.*	After considering the comments received in response to the appraisal consultation document, the committee recommended adalimumab, etanercept and ustekinumab. Please see sections 1 and 4.20 to 4.21 of the final appraisal determination (FAD) for the committee's recommendations and full considerations.
Janssen	**3. Use of incremental analysis of biologics is inconsistent with previous NICE multiple technology appraisals of biologics.** 3.1 The use of incremental analysis to determine which treatments are cost effective is inconsistent with previous multiple technology appraisals (MTAs) of biologics in rheumatoid arthritis, juvenile idiopathic arthritis and psoriatic arthritis, which have taken a pairwise approach to reaching conclusions around the cost effectiveness of biologics compared to best supportive care (BSC). *The consultee submitted further information and references about this comment in its response to consultation. These have not been reproduced here. Please see Committee papers for the full response.*	After considering the comments received in response to the appraisal consultation document, the committee recommended adalimumab, etanercept and ustekinumab. Please see sections 1 and 4.20 to 4.21 of the final appraisal determination (FAD) for the committee's recommendations and full considerations.

Consultee	Comment [sic]	Response
Janssen	**4. The appraisal committee's preferred assumptions regarding carer disutility and higher cost of hospitalisation have not been incorporated in the model and we believe this continues to underestimate the cost effectiveness of biologics** The appraisal committee's preferred assumptions regarding carer disutility and higher cost of hospitalisation have not been incorporated in the model and this continues to underestimate the cost effectiveness of biologics in general and ustekinumab in particular, as the most effective biologic. The inclusion of these additional considerations in the AG model should be undertaken before any final recommendation regarding the cost effectiveness of the biologics is made. *The consultee submitted further information and references about this comment in its response to consultation. These have not been reproduced here. Please see Committee papers for the full response.*	Please see sections 4.14 to 4.15 of the final appraisal determination (FAD) for the committee's recommendations and full considerations.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment [sic]	Response
Royal College of Pathologists	Response from the Royal College of Pathologists: • Has all of the relevant evidence been taken into account? Yes • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? These are fair and reasonable interpretations of the evidence. • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes.	Thank you for your response.

Nominating organisation	Comment [sic]	Response
British Association of Dermatologists	On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal Consultation Document. The British Association of Dermatologists agree with and welcome the recommendations in the ACD for this Multiple Technology Appraisal (MTA).	Thank you for your response.
Psoriasis Association	The Psoriasis Association welcomes the positive recommendations for the use of adalimumab, etanercept and ustekinumab in children with severe psoriasis. Children with severe psoriasis currently have few options, and the fact is that many will have to wait until adulthood for effective treatment. At the Psoriasis Association, we hear from many members and supporters who, after living with severe psoriasis for decades, feel that their lives would have taken a different course had biologic medications been available during their childhoods. We also welcome the fact that disutility of parents and carers, despite being difficult to quantify, has been recognised in this report. The chronic illness of a child can have a substantial impact on the wider family unit, particularly the time-consuming nature of topical regimes, frequent UVB sessions, and regular monitoring required for non-biologic systemics. Without the availability of the biologic treatments being appraised, children and their families have no choice but to rely on these best supportive treatments which would likely have already been tried with sub-par results. It is difficult to measure the impact of this kind of situation accurately, but based on contact with parents of children with psoriasis, we can be sure it is significant.	Thank you for your response.

Nominating organisation	Comment [sic]	Response
The Psoriasis and Psoriatic Arthritis Alliance	Thank you for the opportunity to comment on the ACD for the above appraisal. We welcome the decision to recommend adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people. This is an unmet age group and patients will also welcome a widening of options for those with this with chronic disease. Psoriasis, at any age, is a debilitating disease, and for those who develop the condition at a young age, it needs to be appreciated that they will need a lifetime of therapy, which should be compatible with their life choices. We believe that the committee has taken a pragmatic view based on available evidence, but we would like to urge that caution is observed in the prescribing of these agents, with the longterm benefits and adverse events, monitored and recorded within a registry such as BADBIR.	Thank you for your comment. The NICE team understands that BADBIR now includes children and young people.

Other comments

Nominating organisation	Comment [sic]	Response
NICE Internal comment	The biosimilar etanercept (Benepali, Biogen Idec Ltd) has recently been licensed also for treating plaque psoriasis in children. see SPC here http://www.medicines.org.uk/emc/medicine/31511 *Please note that only internal comments that influenced the committee's decision making are reproduced here.*	Thank you for your comment. Please see section 1.5 and section 4.22 of the final appraisal determination (FAD) for the committee's recommendations and full considerations about biosimilars.

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health

National Institute for Health and Care Excellence

Multiple Technology Appraisal

Psoriasis (plaque, chronic, severe, children, young people) - adalimumab, etanercept and ustekinumab [ID854]

AbbVie's Response to the Assessment Group's Report

7 April 2017

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Dear Meindert,

AbbVie welcomes the opportunity to comment on the appraisal consultation document by the NICE Appraisal Committee for the ongoing multiple technology appraisal of adalimumab, etanercept and ustekinumab in psoriasis (plaque, chronic, severe, children, young people).

Please find our comments summarised below.

With kind regards

[redacted]

[redacted]

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1) **Has all the relevant evidence been taken into account?**

Yes, AbbVie believes that all relevant evidence has been taken into account by the Appraisal Committee in drafting the Appraisal Consultation Document (ACD).

2) **Are the summaries of clinical and cost-effectiveness evidence reasonable interpretation of the evidence?**

Yes, AbbVie believes that the summaries of both clinical and cost-effectiveness evidence included in the ACD are a reasonable interpretation of the evidence

3) **Are the recommendations sound and a suitable basis for guidance to the NHS?**

Yes, AbbVie believes that the recommendations are sound and a suitable basis for guidance to the NHS.

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?**

No, AbbVie does not think there are any aspects of the recommendations that need particular considerations with respect to the factors listed at point 4).

5) **Other comments:**

The wording used in Section 2 of the ACD, page 5, in correspondence to "Prices", should be changed to accurately reflect the SmPC for adalimumab, so to include the words herewith highlighted " [..] or vial for paediatric use", as follows:

"[..] The list prices (excluding VAT; 'British national formulary' [BNF] online, March 2017) are: £352.14 for 40 mg adalimumab in a prefilled pen or prefilled syringe or vial for paediatric use".

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Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people revie [ID854]

anssen response to IC appraisal consultation determination (ACD)
7th April 2017

Janssen welcomes the opportunity to comment on the NICE appraisal consultation document (ACD) for the review of plaque psoriasis in children and young people – adalimumab, etanercept and ustekinumab [ID854].

We welcome the initial positive recommendation for the use of adalimumab, etanercept and ustekinumab for children and young people with severe psoriasis. We agree with the appraisal committee that psoriasis in children and young people significantly impacts their quality of life and can lead to psychosocial problems in their most formative years. We also welcome the committee's overall positive recommendations regarding biologics and their important role in treating severe psoriasis when standard systemic therapies (such as ciclosporin, methotrexate or phototherapy) have failed.

However, we do continue to have concerns regarding some of the economic evidence conclusions in the ACD. We believe the conclusions are not currently consistent with the NICE reference case and continue to cause an equity concern due to the different recommendations between adults and children with severe psoriasis. Overall, we don't believe that ustekinumab represents a less cost effective option when compared to etanercept and that etanercept, adalimumab and ustekinumab all represent cost effective biologics options compared to BSC and should all be recommended as first line biologic options after standard systemic therapies have failed.

Furthermore, we note and welcome the appraisal committee's additional considerations in their decision to recommend biologics. These additional considerations, for example, carer disutility and increased cost of hospitalisation were not captured in the Assessment Group's original economic model. Before the appraisal committee make their final recommendation concerning biologics in children and young people with severe psoriasis, we believe that these additional considerations should be incorporated in the Assessment Group's (AG) economic model to give a robust estimate of the biologics' cost effectiveness.

Overall, we continue to have concerns about the overarching clinical and cost effectiveness conclusions in the ACD and we suggest the following key points should be considered further by the appraisal committee:

1. **Ustekinumab being recommended after the use of etanercept and adalimumab despite the appraisal committee's conclusion that ustekinumab is a more effective treatment option than etanercept. This continues to cause equity concerns regarding access to biologics in children and young people (below 18 years) when compared to adults.**

1.1 Both the network meta-analysis and clinical expert opinion suggested that etanercept is less effective than adalimumab and ustekinumab. We are concerned that both patients and clinicians will not have the option to use ustekinumab despite it being an effective treatment option. Furthermore, this continues to highlight an equity concern regarding equal access to biologics between children and adult with severe psoriasis, as adults will have the option to use ustekinumab as a first line biologic option but children and young people will be denied access.

2. Inconsistency in the appraisal committee's interpretation of the economic incremental analysis regarding etanercept and ustekinumab.

2.1 There appears to be an inconsistent interpretation of the cost effectiveness decision rules in the ACD, specifically including etanercept which is extendedly dominated by adalimumab, but has been recommended as a cost-effective first line biologic treatment option in patients aged 12 and above (population 3). Yet, ustekinumab which currently has an ICER above £30,000 per QALY compared to adalimumab in the incremental analysis has not been recommended as a first line biologic. In our view, all three biologics represent a cost-effective option compared to BSC if a pairwise analysis is undertaken rather than an incremental analysis.

Use of incremental analysis of biologics is inconsistent with previous NICE multiple technology appraisals of biologics.

The use of incremental analysis to determine which treatments are cost effective is inconsistent with previous multiple technology appraisals (MTAs) of biologics in rheumatoid arthritis, juvenile idiopathic arthritis and psoriatic arthritis, which have taken a pairwise approach to reaching conclusions around the cost effectiveness of biologics compared to best supportive care (BSC).

4 The appraisal committee's preferred assumptions regarding carer disutility and higher cost of hospitalisation have not been incorporated in the model and we believe this continues to underestimate the cost effectiveness of biologics

4.1 The appraisal committee's preferred assumptions regarding carer disutility and higher cost of hospitalisation have not been incorporated in the model and this continues to underestimate the cost effectiveness of biologics in general and ustekinumab in particular, as the most effective biologic. The inclusion of these additional considerations in the AG model should be undertaken before any final recommendation regarding the cost effectiveness of the biologics is made.

Overall, we believe that all three biologics (adalimumab, etanercept and ustekinumab) represent cost effective first-line biologic options after systemic therapies have failed in children and young people with severe psoriasis. To avoid potential equity of access issue between children and adults with severe psoriasis, we believe that children should also have access to ustekinumab as a first line biologic option (alongside etanercept and adalimumab). This would ensure the guidance in children and young people are consistent with that of adults with severe psoriasis.

Furthermore, ustekinumab as a first-line biologic option would allow clinicians greater choice and, to maximise patient benefit, we believe that all three biologics should be available for sequential use too. This, in our view, would allow clinicians to optimise the patient treatment pathway based on the patient needs and save the system valuable resources that would otherwise be spent on cycling through biologics that may not be the best treatment option for a patient.

The following sections provide further details on these key points for consideration

anssen response to the IC ACD

1. **Ustekinumab being recommended after the use of etanercept and adalimumab despite the appraisal committee concluding that ustekinumab is a more effective treatment option than etanercept. This continues to raise equity concerns regarding access to biologics in children and young people (below 18 years) when compared to adults**

The results of the network meta-analyses are presented in table 1. The results for PASI 75 showed that the effectiveness of ustekinumab and adalimumab were similar, and that ustekinumab and adalimumab were more effective than etanercept. The committee heard from the clinical expert that this reflected clinical practice because clinicians are unlikely to offer etanercept as a first biological therapy. The committee was concerned that using adult data could potentially bias the effect estimates, but agreed that this was mitigated by the assessment group having adjusted for population and placebo effects. The committee concluded that, despite the uncertainty associated with the network meta-analyses (see section 4.7), they showed adalimumab, etanercept and ustekinumab to be more clinically effective than placebo and methotrexate. In addition, the committee concluded that ustekinumab and adalimumab had broadly similar effectiveness, and that both were more clinically effective than etanercept. [para 4.8]

1.1 Both the network meta-analysis and clinical expert opinion suggested that etanercept is less effective than adalimumab and ustekinumab. We are concerned that both patients and clinicians will not have the option to use ustekinumab despite it being an effective treatment option. Furthermore, this continues to raise an equity concern regarding equal access to biologics between children and adult with severe psoriasis. The recommendation is its current form would mean that adults will have the option to use ustekinumab as first line biologic option but children will be denied access.

We note that the clinical expert in the Appraisal Committee deliberations agreed with the results of the network meta-analysis and further shared that they were unlikely to offer etanercept as a first line option. We are therefore unclear as to why the committee have recommended etanercept as a first line biologic ahead of ustekinumab on this basis. Furthermore, looking at the cost effectiveness of the biologics on a pairwise analysis basis compared to BSC, ustekinumab is a more cost effective option than etanercept (see section 2).

The current recommendation in the ACD for ustekinumab after the failure of at least 1 biologic therapy also raises an equity concern regarding the equal access to biologics between children and adults. This is consistent with our previous concerns raised in the Janssen response to the Technology Appraisal Report (TAR) [27th January 2017] with regards to a consistent recommendation between adults and children. In NICE TA180, ustekinumab for the treatment of adults with moderate to severe psoriasis, ustekinumab is recommended as an option for patients with severe psoriasis without having had to fail at least 1 biologic therapy. We note that appraisal committee's final guidance in TA180:

"*The Committee noted that in the manufacturer's base-case analysis, which included the patient access scheme, ustekinumab had an ICER of £29,600 per QALY gained compared with supportive care, and an ICER of £27,100 per QALY gained compared with etanercept 25 mg given intermittently. The Committee was mindful that this analysis assumed that the cost of intermittent etanercept was 88% of the cost of continuous etanercept. The Committee also noted that the manufacturer's analysis suggested that ustekinumab was less costly and more effective than adalimumab. However, it was aware that revised estimates for the efficacy of adalimumab had been provided during consultation on the ACD, and the resulting ICERs suggested that ustekinumab was not a cost-effective alternative to adalimumab. The Committee considered that the differences in incremental costs and QALYs between all treatments were small, and that this was particularly the case when considering ustekinumab and adalimumab. This meant that these ICERS were very sensitive to small changes in either costs or QALYs and therefore did not represent stable estimates of cost effectiveness.*

Therefore the Committee concluded that no robust differences in cost effectiveness between adalimumab and ustekinumab had been shown." [para 4.18]

From TA180, we note that ustekinumab had an ICER of £29,600 per QALY versus best supportive care in adults. This compares to the ICER of £26,253 per QALY versus BSC in children and young people in the current appraisal. We also note that the appraisal committee in TA180 recognised that ustekinumab was not cost effective compared to adalimumab in the incremental analysis. But noted that there was relatively small difference between costs and QALYs, which made the ICERs unstable.

Likewise, we note the relatively small differences in total costs and QALYs between adalimumab and ustekinumab in this appraisal over the treatment horizon, a difference in total costs of £1,894 and a difference in total QALYs of 0.030. Again, suggesting unstable ICERs which are sensitive to small changes, especially in the QALYs. We are concerned that given the consistency of the results between children and adults appraisals that ustekinumab was recommended in adults as a first line biologic option, but based on similar results in children and young people, ustekinumab has not been recommended as a first line option creating a potential equity concern between children and adult populations.

2. Inconsistency in the appraisal committee's interpretation of the economic incremental analysis regarding etanercept and ustekinumab.

"The committee considered the cost effectiveness of etanercept. It took into account the potential biases associated with the ICER (see section 4.19). The committee recognised that etanercept had an ICER of £8,897 per QALY gained in population 2 but was extendedly dominated in population 3. It further noted that, compared with best supportive care the most plausible ICER was likely to be between £8,897 and £29,177 per QALY gained. The committee therefore concluded that on balance, that etanercept could be considered a cost-effective use of NHS resources" [para 4.22].

"The committee considered the cost effectiveness of ustekinumab. It took into account the potential biases associated with the ICER (see section 4.19). The committee concluded that although a range of biological treatment options was desirable (see section 4.2), the most plausible ICER for ustekinumab was £61,722 per QALY gained (compared with adalimumab), and ustekinumab was associated with higher costs that the other technologies. The committee agreed that ustekinumab could not be considered a cost-effective use of NHS resources. The committee tried to identify a subgroup in whom ustekinumab would be cost effective. The committee recognised that, although only a small proportion of people in CADMUS had previous biological therapy (up to 14% of patients in CADMUS), ustekinumab could also be considered in children and young people with severe psoriasis whose disease has not responded to standard systemic therapy and at least 1 biological therapy, for example, adalimumab or etanercept, because this would likely reflect a group of high unmet need. The committee agreed that the ICER for ustekinumab compared with best supportive care was £26,253 per QALY gained and that this would be the most appropriate comparison for people with severe psoriasis whose disease had not responded to at least 1 biological treatment. The committee concluded that ustekinumab could be considered a cost effective use of NHS resources for this population" [para 4.24].

2.1 There appears to be an inconsistent interpretation of the cost effectiveness decision rules in the ACD, specifically including etanercept which is extendedly dominated by adalimumab, but has been recommended as a cost-effective first line biologic treatment option in patients aged 12 and above (population 3). Yet, ustekinumab which currently has an ICER above £30,000 per QALY compared to adalimumab in the incremental analysis has not been recommended as a first line biologic. All three biologics represent a cost-effective option compared to BSC if a pairwise analysis is undertaken rather than an incremental analysis.

We believe that the interpretation of the economic evidence in the ACD is currently being applied inconsistently across the three biologics and is not in line with the NICE reference case and standard

economic decision rules. The NICE reference case states that 'standard decision rules should be followed when combining costs and QALYs. When appropriate, these should reflect when dominance or extended dominance exists, presented thorough incremental cost–utility analysis (NICE Methods guide, 2013).' We note that in the NICE ACD, the appraisal committee appear to have made their decision not to recommend ustekinumab as a first line biologic in population 3 based on the incremental analysis. However, in contrast, for etanercept the appraisal committee have not used the incremental analysis and appear to have based their decision on a pairwise analysis compared to BSC when making their decision to recommend etanercept as a first line biologic option in population 3.

In the incremental analysis, we note that etanercept is extendedly dominated by adalimumab. On this basis, etanercept should not be recommended as a first line biologic, as adalimumab represents a better use of NHS resources than etanercept based on the standard decision rules stipulated in the reference case. The final decision by the committee in population 3 appears therefore to be based on the pairwise comparison or etanercept versus BSC being cost effective (£29,177 per QALY) and not the incremental analysis where etanercept was extendedly dominated by adalimumab; see table 1 below for the full incremental and pairwise results.

Table Combined impact of alternative assumptions on the cost effectiveness of the interventions after failed systemic therapy (Adult utility (TA 4) 48 hospitalisation per annum) Reproduced from the technology appraisal report (TAR), Table 98, pg. 233)

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental analysis (ICER)	Pairwise analysis vs. BSC (ICER)
BSC	32,333	4.351	-	-	-	-
ETA	40,102	4.618	7.769	0.266	ED ADA	29,177
ADA	43,193	4.807	10.860	0.455	23,861	23,861
UST	45,087	4.837	1.894	0.031	61,722	26,253

If the same reasoning was applied to ustekinumab, then ustekinumab would represent a more cost effective option compared to etanercept in population 3 (based upon the pairwise ICER for ustekinumab versus BSC of £26,253 per QALY being lower than the pairwise ICER for etanercept versus BSC £29,177 per QALY in population 3). Bearing in mind that ustekinumab is not a licensed treatment in population 2 and therefore no equivalent ICER is available for ustekinumab in this population, if standard NICE decision rules concerning extended dominance are not 'appropriate' in this appraisal as stated in the NICE reference case, then we would ask the NICE appraisal committee to use pairwise analysis to determine whether ustekinumab represents a cost-effective use of resources as first line biologic for children and young people with severe psoriasis when compared to BSC, on the same basis as etanercept.

Use of incremental analysis of biologics is inconsistent with previous NICE multiple technology appraisals of biologics.

The use of incremental analysis to determine which treatments are cost effective is inconsistent with previous multiple technology appraisals (MTAs) of biologics in rheumatoid arthritis, juvenile idiopathic arthritis and psoriatic arthritis, which have taken a pairwise approach to reaching conclusions around the cost effectiveness of biologics compared to best supportive care (BSC).

We note that previous NICE appraisal committees in previous MTAs have also found it not appropriate to consider standard decisions rules when considering the economic evidence concerning biologics. In previous NICE appraisals for biologics in psoriatic arthritis, juvenile idiopathic arthritis and rheumatoid arthritis, pairwise analyses of biologics compared to best supportive care or standard of care treatments such as methotrexate have been considered for decision making purposes. In NICE TA199, TA373, and TA375, NICE have recommended biologics consistently if they have demonstrated cost effectiveness through a pairwise analysis compared to the standard of care, such as methotrexate.

We note that in TA373 for abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis the following was stated:

"The Committee noted that the Assessment Group had presented pairwise comparisons of each of the 4 technologies with methotrexate rather than a fully incremental analysis in its base case. The committee considered other biological treatments, and not methotrexate, would be the most clinically relevant comparator if biological treatments continued to be available in clinical practice. However, if biological treatments were not available, methotrexate would be the only treatment option available to patients. The Committee agreed that differences between the clinical trials for the 4 technologies prevented a robust comparison between the technologies in the indirect treatment comparison. Moreover, the Committee noted that it had not been presented with evidence of a difference in the clinical effectiveness of the biological treatments in clinical practice. For these reasons the Committee considered the pairwise comparisons of cost effectiveness between each technology and methotrexate appropriate for its decision-making. The Committee noted that taking into account the patient access schemes for abatacept and tocilizumab resulted in base-case ICERs of around £30,000 to £40,000 per QALY gained for adalimumab, etanercept and tocilizumab compared with methotrexate in the '1st biologic model' and around £30,000 to £36,000 per QALY gained for abatacept, adalimumab, etanercept and tocilizumab compared with methotrexate in the '2nd biologic model'. The Committee considered the Assessment Group's scenarios tested in the '1st biologic model': assuming that people with remission stop treatment; assuming that the health resource costs differ when on methotrexate or a biological treatment; assuming that caregivers experience a decrease in quality of life; and assuming a younger starting age in the model; the Committee considered all these more plausible than the Assessment Group's base-case analysis. Applying these assumptions individually resulted in lower ICERs for all 3 technologies (adalimumab, etanercept and tocilizumab) compared with methotrexate than the base case. The Committee agreed that the discounting rates in the current NICE reference case should be applied in the model. The Committee also noted that, in the '2nd biologic model', the only assumption the Assessment Group had tested was around the younger starting age, which decreased the ICER for all 4 technologies compared with methotrexate in this model. It considered that this scenario was more plausible than the Assessment Group's base case in the '2nd biologic model'. The Committee concluded that the Assessment Group's scenario assumptions (except a scenario that used a different discount rate to the current NICE methods guide) were appropriate and should be applied." [para 4.48]

We firmly believe that this interpretation of the evidence should also apply to this appraisal. In the absence of any biologics, best supportive care (consisting of methotrexate) would be the only treatment option available to these patients. We strongly feel that if the same reasoning was to be applied to the current appraisal, then ustekinumab would also represent a cost-effective option as a first line biologic treatment, with an ICER of £26,253 per QALY compared to the BSC as demonstrated above.

4 The appraisal committee's preferred assumptions regarding carer disutility and higher cost of hospitalisation have not been incorporated in the model and we believe this continues to underestimate the cost effectiveness of biologics.

4 The appraisal committee's preferred assumptions regarding carer disutility and higher cost of hospitalisation have not been incorporated in the model and this continues to underestimate the cost effectiveness of biologics in general and ustekinumab in particular. , The inclusion of these additional considerations in the AG model should be undertaken before any final recommendation regarding the cost effectiveness of the biologics is made.

We understand that the appraisal committee have taken additional considerations such as carer disutility and higher cost of hospitalisation into account in making their recommendation regarding the use of biologics in this population. However, we believe that the relative cost effectiveness of biologics remains uncertain and is likely to be underestimated, particularly for the most effective treatments, adalimumab and ustekinumab. This puts ustekinumab in a position of disadvantage overall, as ustekinumab is the most effective biologic. We agree with the appraisal committee that the carer disutility should be incorporated into the decision, and the conclusion that including carer disutilities may reduce the ICERs for more effective treatments like ustekinumab. We further agree with the appraisal committee that using higher costs for hospitalisation and for treatment at day centres might reduce the ICERs for more effective treatments even further. Overall, we firmly believe that incorporating carer disutility and revised hospitalisation costs (offset slightly by reducing the number of hospitalisation below 6.49 days) in the economic model would be a reasonable way forward.

If these changes were to be incorporated in the economic modelling, we firmly believe that the cost effectiveness of ustekinumab relative to BSC and the other biologics in population 3 is likely to further improve. These changes to the economic model should be included before any final recommendation regarding the relative cost effectiveness of biologics is made. We continue to believe that ustekinumab is a cost-effective option compared to the BSC, alongside etanercept and adalimumab, and should be recommended as a first line biologic accordingly.

Conclusion

Overall, we believe that all three biologics (adalimumab, etanercept and ustekinumab) represent cost effective options as first line biologic treatment options for severe psoriasis in children and young people. There should be no inequity in access to biologics in this population compared to the adult population. Furthermore, to aid clinician choice and maximise patient benefit, we believe that all three treatments should be available for sequential use as first line biologic treatment options.

eferences

- Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis. Technology appraisal guidance Published: 16 December 2015. Available from www.nice.org.uk/guidance/ta373 Date accessed 3rd April 2017

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- Adalimumab, etanercept, inflfliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Technology appraisal guidance. Published: 26 January 2016. Available from: www.nice.org.uk/guidance/ta375 Date accessed 3rd April 2017.

- NICE Guide to the methods of technology appraisal 2013. Process and methods [PMG9] Published date: April 2013. Available from https://www.nice.org.uk/process/pmg9/chapter/foreword. Date accessed 27th January 2017.

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4th April 2017

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people

To whom it may concern,

The Psoriasis Association welcomes the positive recommendations for the use of adalimumab, etanercept and ustekinumab in children with severe psoriasis. Children with severe psoriasis currently have few options, and the fact is that many will have to wait until adulthood for effective treatment. At the Psoriasis Association, we hear from many members and supporters who, after living with severe psoriasis for decades, feel that their lives would have taken a different course had biologic medications been available during their childhoods.

We also welcome the fact that disutility of parents and carers, despite being difficult to quantify, has been recognised in this report. The chronic illness of a child can have a substantial impact on the wider family unit, particularly the time-consuming nature of topical regimes, frequent UVB sessions, and regular monitoring required for non-biologic systemics. Without the availability of the biologic treatments being appraised, children and their families have no choice but to rely on these best supportive treatments which would likely have already been tried with sub-par results. It is difficult to measure the impact of this kind of situation accurately, but based on contact with parents of children with psoriasis, we can be sure it is significant

Yours faithfully,

[redacted]

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5 April 2017

Meindert Boysen
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Dear Meindert

Multiple Technology Appraisal (MTA)
Adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people [ID854]
Appraisal Consultation Document

Thank you for the opportunity to comment on the ACD for the above appraisal.

We welcome the decision to recommend adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people.

This is an unmet age group and patients will also welcome a widening of options for those with this with chronic disease.

Psoriasis, at any age, is a debilitating disease, and for those who develop the condition at a young age, it needs to be appreciated that they will need a lifetime of therapy, which should be compatible with their life choices.

We believe that the committee has taken a pragmatic view based on available evidence, but we would like to urge that caution is observed in the prescribing of these agents, with the long-term benefits and adverse events, monitored and recorded within a registry such as BADBIR.

Yours sincerely

[redacted]

British Association of Dermatologists
Response to NICE Appraisal Consultation Document
On the Multiple Technology Appraisal (MTA)
Adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people [ID854]

British Association of Dermatologists
Therapy & Guidelines and BADBIR sub-committees

On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal Consultation Document.

The British Association of Dermatologists agree with and welcome the recommendations in the ACD for this Multiple Technology Appraisal (MTA).

[redacted]
[redacted]

Adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people [ID854] Appraisal Consultation Document

Response from the Royal College of Pathologists

- Has all of the relevant evidence been taken into account?
  Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
  These are fair and reasonable interpretations of the evidence.

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

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people

Assessment Group Report Addendum

12th April 2017

Overview

Following the first appraisal meeting of adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people (22nd February 2017), the Assessment Group (AG) prepared an addendum with additional explanation and analyses in response to the Appraisal Consultation Document (ACD). The response below is based on two concerns:

1. Uncertainty about how adult utility data was incorporated into the economic model; and
2. Cost-effectiveness results for the committee's preferred assumptions.

Uncertainty about how adult utility data was incorporated into the economic model

The ICERs reported in the ACD relate to the use of TA 146 adult utility values (see Table 98 of the AG report). These utility values represent the more favourable gains in utility from baseline for each of the PASI response categories compared to those reported in other adult appraisals. The committee indicated that they were unclear about how the adult utility values were incorporated into the scenario analysis. There are two components to the utility values: (1) the baseline utility value and (2) the utility gain from baseline by PASI response category (PASI<50, 50-75, 75-90, ≥90). The proportion of individuals in the different PASI response categories for the treatments is based on the results of the network meta-analysis (NMA). This means that PASI response rates are assumed to be a perfect proxy for change in utility arising from treatment. The adult utility values were incorporated into the model in the same way as the utility values for children and young people; the only difference is that the utility values changed for both baseline utility and gains from baseline by PASI response category. Table 1 compares the baseline utility value and mean change in EQ-5D utility by PASI response category for adults (TA 146) and children and young people.

Table 1: Baseline utility and mean change in EQ-5D by PASI response category for adults (TA 146) and children and young people.

	Baseline utility	Gain in utility from baseline by PASI response category			
		PASI <50	PASI 50-75	PASI 75-90	PASI ≥90
Children and young people	0.860	0.0036	0.0255	0.0340	0.0810
Adults (TA146)	0.692	0.063	0.178	0.178	0.308

The committee suggested that there may be other methodologies to incorporate the adult utility values into the model. In particular, it was suggested that the proportional change in utility from baseline by PASI response category in adults could be applied to the baseline utility in children and young people. The AG notes that this would result in the absolute utility values in children and young people going above one (see Table 2). If the values were constrained to one, there would be no difference between the utility values for PASI response rates greater than 50 (and therefore limited differences in QALYs between the interventions).

Table 2: Utility values in children and young people adjusted for the proportional change from baseline observed in adult utility values (TA 146).

	Utility by PASI response category			
	PASI <50	PASI 50-75	PASI 75-90	PASI ≥90
Proportional change from baseline in adults	9.104%	25.72%	25.72%	44.51%
Adjusted absolute utility values in children and young people*	0.938295	1.081214	1.081214	1.242775

*Adjusted for the proportional change from baseline in adults and applied to the baseline in children and young people

It might be tempting to constrain the absolute value for the PASI ≥90 category to one and then adjust the other PASI utility values by the proportional change from baseline in adults; however, this would ultimately reduce the baseline utility value in children and young people down to the same value as in adults (0.692). The corresponding cost-effectiveness results would be the same as those derived from TA 146. It is also worth noting that the baseline utility value only alters the total absolute number of QALYs – it doesn't affect the relative cost-effectiveness of the interventions (since the baseline utility value is the same regardless of treatment), whereas it is the gain in utility from baseline by PASI response category that affects the relative cost-effectiveness of the interventions.

Cost-effectiveness results for the committee's preferred assumptions

The committee's preferred assumptions include:

- Using adult utility values (TA 146) for children and young people;
- Assuming that the likely number of days in hospital with best supportive care is between 0 and 6.49 days per annum;
- Using higher costs for hospitalisations and for treatment of day centres based on paediatric codes;
- Including carer utilities.

The scenario analysis presented in the AG report considers the use of adult utility values from TA 146 and the higher rate of hospitalisations of 6.49 days per annum based on Fonia et al (see Table 98 of the AG report). The AG acknowledges that there may be potential benefits to treatment that fall outside the QALY calculation (e.g. carer utilities). However, there are no quantitative estimates of the impact on the health related quality of life of carers for children and young people with psoriasis who receive adalimumab, etanercept or ustekinumab. In the absence of quantitative estimates of these potential benefits, the AG is unable to incorporate these into the economic analysis. Any attempt to add arbitrary values to the utility estimates that are already highly uncertain will introduce further uncertainty.

The unit cost for inpatient bed day in the AG base-case analysis (£295.80) corresponds to the average unit cost of a non-elective excess bed day in the NHS across all HRG codes. The higher cost for paediatric inpatient stay is £520.68 per bed day. However, it is unclear whether this unit cost also includes costs related to treatment. Treatment costs are included separately in the cost of BSC via its other components (drugs, monitoring, and phototherapy costs). The day centre cost included in the AG base-case analysis refers to skin disorders without interventions (£472.55). The cost of treatment (e.g. phototherapy sessions) is considered separately in the cost of BSC. The paediatric day centre cost of £622.29 does not separate between skin disorders with and without intervention, which may lead to potential double counting of treatment costs. The committee's preferred assumption is to use the paediatric inpatient stay cost of £520.68 per bed day and the paediatric day centre cost of £622.29.

Table 3 presents the cost-effectiveness results based on the committee's preferred assumptions of adult utility values (TA 146), 6.49 hospitalisation days per annum (best case scenario of committee's preferred assumptions), and paediatric costs for inpatient stay and day centre.

Table 3: Cost-effectiveness results using adult utility values (TA146), 6.49 hospitalisations per annum, and paediatric costs for hospitalisations and day centre cases.

Adalimumab as an alternative to systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Population 1: Children and young people – starting age 4 years						
MTX	72,263	9.228	-	-	-	MTX
ADA	94,498	9.489	22,235	0.261	85,170	

ADA, adalimumab; MTX, methotrexate.

Interventions after failed systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Population 2: Children and young people - starting age 6 years							
BSC	77,672	7.890	2,237	-0.327	Dominated	-	ETA
ETA	75,434	8.217	-	-	-	Dominant	
ADA	84,671	8.451	9,237	0.234	39,410	12,466	
Population 3: Children and young people – starting age 12 years							
BSC	44,507	4.351	-	-	-		ADA
ETA	48,053	4.618	3,546	0.266	ED ADA	13,324	
ADA	49,341	4.806	4,834	0.455	10,624	10,624	
UST	50,996	4.837	1,655	0.030	54,381	13,368	