National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

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

Response to consultee and commentator comments on the draft remit and draft scope (post-referral)

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.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AbbVie Limited	Yes	Comment noted. No action required.
	British Association of Dermatologists	Yes. Presently there are no biological therapies with NICE approval for the treatment of psoriasis in children.	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.
	Psoriasis Association	Whilst it is important for children and adolescents to have the most appropriate treatments available to them, it is a relatively small population of children or adolescents who would require treatment with these drugs for their psoriasis. In most cases, children or adolescents with psoriasis severe enough to warrant treatment with one of the named drugs should be under the care of a supra or tertiary specialist, who are likely to use these drugs	Comment noted. No action required.

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		where appropriate, whether there is guidance or not. To conclude, this topic is appropriate for a NICE appraisal, but may not be the most urgent aspect of guidance needed for this population.	
Wording	AbbVie Limited	Yes	Comment noted. No action required.
	British Association of Dermatologists	Yes	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.
Timing Issues	AbbVie Limited	This appraisal should be treated as a priority as, unlike adults, currently children with psoriasis are unable to access biologic treatments.	Comment noted. No action required.
	British Association of Dermatologists	Urgent; with the licensing of three biological therapies for use under 16 years of age this has now become very important.	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.
	Psoriasis Association	Medium-low urgency, given the small number of children and adolescents with psoriasis severe enough to warrant the use of these drugs. The population of children and adolescents with all severities of psoriasis is much larger and it may be that guidance is required more urgently around	Comment noted. As adalimumab, etanercept and ustekinumab are now licensed for

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		interventions for children and young people with mild to moderate disease.	children and young people, and other consultees view this appraisal as important, it has been scheduled into the NICE work programme.
Additional comments on the draft remit	AbbVie Limited	None	Comment noted. No action required.
	British Association of Dermatologists	None of the standard systemic therapies, used to treat psoriasis in children are licensed for use for this indication.	Comment noted. No action required.
	Janssen	No further comment.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AbbVie Limited	No further comments	Comment noted. No action required.
	British Association of Dermatologists	None	Comment noted. No action required.

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	Janssen	No comment.	Comment noted. No action required.
	Psoriasis Association	It could be of benefit to consider the Parisi et al study (2013) alongside the referenced Gelfand study (2005). (Journal of Investigative Dermatology (2013) 133, 377-385)	Comment noted. Parisi et al (2013) does not provide information about the prevalence of psoriasis in children in the United Kingdom.
The technology/ intervention	AbbVie Limited	Yes	Comment noted. No action required.
	British Association of Dermatologists	Yes. It is likely that data for secukinumab will be available in the next two years.	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.
	Psoriasis Association	As far as we are aware, yes.	Comment noted. No action required.
Population	AbbVie Limited	Due to the differences in marketing authorisation regarding age ranges between the biologics under review, children and young people should be considered as separate populations.	Comment noted. The other considerations section of the scope has been updated to include potential subgroups defined by age.
	British Association of Dermatologists	Yes	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.

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	Psoriasis Association	It could be beneficial to further define "children" and "adolescents", and consider making different recommendations within this MTA as there is a big difference in treating a 6 year old with these drugs compared to a 16 year old. Although this MTA focusses on the treatment of psoriasis, it would also be beneficial to note that children and young people with psoriasis may be experiencing symptoms of diagnosed or undiagnosed psoriatic arthritis, which may also be impacted by the use of these treatments.	Comment noted. The NICE style guide defines children as aged up to 16 years and young people as aged 16 and 17 years. The Other considerations section of the scope has been updated with potential subgroups for age.
Comparators	AbbVie Limited	Include adalimumab within the biological treatment to be used outside of their marketing authorisation: Biological treatments used outside of their marketing authorisation (such as infliximab, adalimumab, etanercept or ustekinumab if used outside of the constraints of the relevant marketing authorisation in children and young people)	Comment noted. The comparators section of the scope has been updated. Adalimumab has been added as an example for biological treatments used outside of their marketing authorisation.
	British Association of Dermatologists	Yes, with the caveat that the standard systemic agents are not licensed for use in this group.	Comment noted. No action required.
	Janssen	The scope mentions topical treatment; Janssen does not consider topical treatment to be a relevant comparator given the treatment positioning of all biological therapies considered in this appraisal is post-topical treatments, as per the licensed wording of each therapy. Both ustekinumab and etanercept are indicated for use	Comment noted. Guidance will only be issued in accordance with the marketing authorisation. At the scoping workshop, attendees agreed that despite differences in the wording of the marketing authorisations for the biologic treatments, they could

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		following systemic treatments; however, adalimumab has an indication at the systemic treatment level in the treatment pathway. Consequently, Janssen consider systemic treatments to be a relevant comparator only to adalimumab, and not an appropriate comparator for ustekinumab and etanercept. Janssen does not believe that it is appropriate to consider comparing to infliximab or infliximab biosimilars as these compounds do not have an adolescent indication. Furthermore, after a pragmatic search of the literature, Janssen does not believe that there are any relevant data to assess the use of infliximab or infliximab biosimilars for the discussed indication. Similarly, Janssen does not believe that there is any relevant data available to assess the use of the reviewed medicines for any off licence use and as such does not believe it relevant to consider these comparisons as part of this review process.	potentially be used at similar positions in the treatment pathway. Attendees also agreed that topical therapies should be added to the list of comparators for people in whom non-biological systemic treatments are not suitable. Responses to consultation from other stakeholders suggested that infliximab and infliximab biosimilars are suitable comparators; accordingly, these comparators have been retained in the scope.
	Psoriasis Association	The comparators considered are appropriate. Infliximab could be considered in some circumstances owing to its paediatric experience in treating Juvenile Idiopathic Arthritis (and so biosimilars inflectra and remsina may need to be considered).	Comment noted. No action required. The economic analysis section of the scope states that the availability and cost of biosimilars should be taken into account.
Outcomes	AbbVie Limited	The ability to attend school and participate in usual daily activities should be included.	Comment noted. The outcomes currently described in the scope should capture the impact on usual

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		In addition, the quality of life and impact on caregivers (e.g. parents) should be included. Consider using the outcome measure reduction in severity of psoriasis	daily activities. Companies can submit evidence on outcomes considered clinically relevant to this appraisal. The NICE reference case includes the quality of life impact on carers (see section 5.1.7–5.1.10 of the guide to the methods of technology appraisal). The reduction in severity of psoriasis is covered by the outcomes listed in the scope.
	British Association of Dermatologists	In children, the cDLQI has become the gold standard for assessment of quality of life impact. A PGA or a PASI 90/ 75 or minimal or clear disease would be used for disease severity. The PASI was never validated in the paediatric population but has become the gold standard for adults.	Comment noted. NICE scopes do not usually specify the outcome measure (such as a specific questionnaire). The broad outcomes listed in the scope can include disease-specific outcomes (such as the Children's Dermatology Life Quality Index).
	Janssen	No comment.	Comment noted. No action required.
	Psoriasis Association	We support the use of the Children's Dermatology Life Quality Index as a health-related quality of life measure as it includes key areas of impact for this age group, in particular school, sleep and itch, plus socialising. However, it may be beneficial to use outcome measure that cover these key areas in greater depth. The social / psychological benefits associated with these drugs must not be overlooked in this population. Being	Comment noted. Comment noted. NICE scopes do not usually specify the outcome measure (such as a specific questionnaire). The broad outcomes listed in the scope can include disease-specific outcomes (such as the Children's Dermatology

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		able to achieve disease control at an early age could have significant positive effects on their education, social development and future careers, as well as mental health. It is important to capture the views of the patients and carers in this population. Again, children and young people could be experiencing symptoms of diagnosed or undiagnosed psoriatic arthritis, and so it could be beneficial to include any effect on the joints as an outcome measure.	Life Quality Index). The NICE reference case includes the quality of life impact on carers (see section 5.1.7–5.1.10 of the guide to the methods of technology appraisal). Companies can submit evidence on outcomes considered clinically relevant to this appraisal.
Economic analysis	AbbVie Limited	The economic burden of psoriasis on children can be considerable as its onset can be at a critical time of a child's development and can affect their education and future work productivity. In addition, the disease has an impact on parent/carer productivity. Given that the majority of the burden of psoriasis is likely to be borne by patients and caregivers rather than the health care system, AbbVie considers that a societal perspective should be considered in this appraisal.	Comment noted. The reference case stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (such as carers). The perspective adopted on cost should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.1.7–5.1.10 of the guide to the methods of technology appraisal.

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	British Association of Dermatologists	Appropriate.	Comment noted. No action required.
	Janssen	No comment.	Comment noted. No action required.
Equality and Diversity	AbbVie Limited	No issues identified	Comment noted. No action required.
	British Association of Dermatologists	Children with psoriasis may have inflammatory bowel disease as well as the JIA variant of psoriatic arthritis. Obviously children are more likely to prefer oral medication than an injection.	Comment noted. The Committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.
	Janssen	No comment.	Comment noted. No action required.
Other considerations	AbbVie Limited	None	Comment noted.
	British Association of Dermatologists	None	Comment noted.
	Janssen	Following a pragmatic search of the literature, Janssen does not believe that there are any relevant data to assess the use of the reviewed therapies in the suggested subgroups as listed in the draft scope.	Comment noted. The scope states that subgroups should be analysed if evidence allows.

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	Psoriasis Association	It could be beneficial to further define "children" and "adolescents", and consider making different recommendations within this MTA, as there is a big difference in treating a 6 year old with these drugs compared to a 16 year old.	Comment noted. The NICE style guide defines children as aged up to 16 years and young people as aged 16 and 17 years. The other considerations section of the scope has been updated to include potential subgroups defined by age.
Innovation	AbbVie Limited	There are likely to be health related benefits that are not captured by the QALY calcluation given that modelling based on the extrapolation of functional benefits (PASI improvements) may not capture the long term benefits of treatment on a child's development. These may be the main benefits of treatment with adalimumab.	Comment noted. The appraisal committee will discuss the potentially innovative nature of these technologies.
	British Association of Dermatologists	This would be a step-change in paediatric care since there are no biological therapies currently licensed for use. There are now published trials for etanercept, ustekinumab and adalimumab.	Comment noted. The appraisal committee will discuss the potentially innovative nature of these technologies.
	Janssen	There is an unmet need for agents with an alternative mechanism of action (MoA) to current treatments for the treatment of moderate to severe plaque psoriasis in the adolescent population. Ustekinumab indeed has a different MoA to currently licensed TNF-α treatments for PsO. Moreover, ustekinumab has the least frequent dosing regimen	Comment noted. The appraisal committee will discuss the potentially innovative nature of these technologies.

<table>
<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
<tr><td></td><td></td><td>compared to all approved PsA treatments (see table below). This means that, with ustekinumab, fewer injections are required for PsA patients or the NHS to administer, compared with TNF-α inhibitors.

Treatment dosing regimens

<table>
<tr><th>Mechanism of action</th><th>Treatment</th><th>Dose / frequency</th><th>Injections p.a. as maintenance</th></tr>
<tr><td rowspan="2">TNF-α inhibitors</td><td>Adalimumab</td><td>40 mg every other week</td><td>26</td></tr>
<tr><td>Etanercept</td><td>50 mg once weekly</td><td>52</td></tr>
<tr><td>IL-12/IL-23 inhibitor</td><td>Ustekinumab</td><td>Week 0, 4, 16, then every 12 weeks thereafter</td><td>4 or 5</td></tr>
</table>

Stelara is available via homecare with the option of a nurse to help with administration and dose calculation.</td><td></td></tr>
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	Psoriasis Association	Etanercept has had its paediatric marketing authorisation for a number of years (2009) and so it is perhaps not innovative. However, adalimumab and ustekinumab have held paediatric marketing authorisation for much shorter periods of time, and so do represent new treatment options for children and young people. Ustekinumab works quite differently from the two anti-TNFs, and so this does represent a novel treatment option for children and young people. The option of three different biologic treatments, rather than just etanercept, offers hope to children and young people who have not experienced acceptable results on the use of their first biologic.	Comment noted. The appraisal committee will discuss the potentially innovative nature of these technologies.
Questions for consultation	AbbVie Limited	*Is the treatment pathway for moderate plaque psoriasis different to the treatment pathway for severe plaque psoriasis?* It is difficult to define severity in a paediatric population as there are no validated severity measures available in children and young people. Without the ability to determine disease severity in this population it is difficult to answer this question. *Would adalimumab, etanercept and ustekinumab be used at the same position in the treatment pathway for children and young people with plaque psoriasis?* The 3 biologics under consideration have different ages	Comment noted. No action required. Comment noted. The other considerations section of the scope has been updated to include potential subgroups defined by age.

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		within their marketing authorisation (ADA from 4 years, ETN from 6 years and UST from 12 years). In addition adalimumab is the only biologic with a licence to treat prior to systemic therapy which would indicate that based on the marketing authorisation, each biologic would have a different position within the treatment pathway	
		Are the listed outcomes relevant and defined appropriately? Are there any additional outcomes that are not currently listed? We suggest using the outcome measure reduction in severity of psoriasis	Comment noted. The outcomes currently described in the scope can include reduction in severity
		Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom adalimumab, etanercept and ustekinumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Due to the differences in marketing authorisation regarding age ranges between the biologics under review, children and young people should be considered as separate populations.	Comment noted. The other considerations section of the scope has been updated to include potential subgroups defined by age.

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	British Association of Dermatologists	Currently there is no formal treatment pathway for children as many of the therapeutic interventions are not licensed under 16 years of age. These children are treated, largely in line with pathways for adult disease as the draft scope indicates. There is limited off-license use of biological therapies in the NHS in young people with severe psoriasis who have failed standard systemic therapy. Due to the licensing restriction of the biological therapies, this was generally using etanercept as a first line biological agent. However, now adalimumab and ustekinumab are licensed this may change, especially since children would prefer fewer injections to gain disease control. It will be difficult to get good quality data to compare biological therapies as treatment modalities in this group. However, not all patients respond to the same therapeutic intervention and it would be important not to restrict choice or the sequential use of these agents in cases where there was primary or secondary failure. The outcome measures should be for minimal or clear disease and health-related quality of life measures. The PASI 75 or 90 is also useful but not validated for use in children although the published RCTs have used this outcome measure.	Comment noted. No action required. Comment noted. No action required. Comment noted. The outcomes currently described in the scope can include disease specific outcomes (such as PASI 75 or 90) and reduction in severity.

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	Janssen	**For children and young people with moderate plaque psoriasis:** **Which treatments are used in the NHS?** - Currently, there are four systemic treatments in paediatric PsO, methotrexate, ciclosporine, retinoids(acitretin) and fumaric acid esters (fumaderm). Methotrexate, ciclosporine are widely used; however, acitretin has some restrictions to use and there is limited data for Fumaderm. - Infliximab is rarely used. Infliximab has a paediatric licence for Crohn's disease but not psoriasis. There are limited robust data, including few case studies for the use of infliximab in the considered indication.	Comment noted. No action required.
		Does the treatment pathway vary depending on the age of the child or young person? - Janssen anticipates that medicines are prescribed in line with their relevant licences, which detail age restrictions.	Comment noted. The other considerations section of the scope has been updated for potential subgroups for age.
		Is the treatment pathway for moderate plaque psoriasis different to the treatment pathway for severe plaque psoriasis? - Janssen does not believe that there are noticeable differences in the current treatment pathways for moderate and severe plaque psoriasis and anticipates that biological therapies will be used in line with their relevant licences.	Comment noted. No action required. Comment noted. No action required.

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		Would adalimumab, etanercept and ustekinumab be used at the same position in the treatment pathway for children and young people with plaque psoriasis? - Janssen anticipates that adalimumab, etanercept and ustekinumab will be used in line with their relevant licences. **Have all relevant comparators for adalimumab, etanercept and ustekinumab been included in the scope?** - Please see comments above (pg. 2). **Are the listed outcomes relevant and defined appropriately? Are there any additional outcomes that are not currently listed?** - No further comment. **Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom adalimumab, etanercept and ustekinumab are expected to be more clinically effective and cost effective or other groups that should be examined separately?** - Please see comments above (pg. 3). **Where do you consider adalimumab, etanercept and ustekinumab will fit into the existing NICE pathway for psoriasis?** - Janssen anticipates that adalimumab, etanercept and ustekinumab will be used in line with their relevant licences.	Comment noted. Please see the response to the comparators section above. Comment noted. No action required. Comment noted. Please see the response to the other considerations section above. Comment noted. No action required. Comment noted. The reference case

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		Do you consider that the use of adalimumab, etanercept or ustekinumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? - The frequency and method of administration of biological therapies differs and the impact that this will have on patients' lives may not be captured through traditional QoL and economic modelling approaches. For more information see page 3.	stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (such as carers). If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.1.7–5.1.10 of the Guide to the methods of technology appraisal.
	Psoriasis Association	In reality, adalimumab and etanercept would probably be used at the same position in the treatment pathway, however the marketing authorisation for adalimumab allows it to be used earlier in the pathway, and in younger children. Similarly, ustekinumab's marketing authorisation of adolescents rather than children means it may be used at a later point in the pathway. Defining children and adolescents and examining them as different subgroups could be of use – it may be that, in reality, the criteria and severity of disease that may justify the use of a biologic drug in an adolescent may be different for that of a child. The social / psychological benefits associated with these drugs	Comment noted. No action required. Comment noted. The other considerations section of the scope has been updated to include potential subgroups defined by age.

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		must not be overlooked in this population. Being able to achieve disease control at an early age could have significant positive effects on their education, social development and future careers, as well as mental health. We welcome an MTA approach on this occasion.	Comment noted. The outcomes currently described in the scope can include outcomes for usual daily activities and mental health.
Additional comments on the draft scope	AbbVie Limited	No additional comments	Comment noted. No action required.
	British Association of Dermatologists	None not already raised.	Comment noted. No action required.
	Janssen	No further comment.	Comment noted. No action required.
	Psoriasis Association	It is important to have appropriate drugs available to all age groups, but of paramount importance is that the patients can access the relevant healthcare professions / specialist when needed. For example, a child with severe psoriasis must be seen in the most appropriate centre (in many cases tertiary care), from where they can access the most appropriate drugs. The NICE guideline for the assessment and management of psoriasis (CG153) recommends that children and young people with any type of psoriasis should be referred from primary care to a specialist – this recommendation should be upheld and highlighted.	Comment noted. No action required.
	The Royal College of Physicians	We would like to formally endorse the response submitted by the British Association of Dermatologists.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Napp Pharmaceuticals

Pfizer

The Department of Health

The Royal College of Nursing