National Institute for Health and Care Excellence

Health Technology Evaluation

Ublituximab for treating relapsing multiple sclerosis ID6350

Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Biogen Idec	Single technology appraisal route is appropriate	Comments noted. A cost comparison route has been chosen to evaluate if the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology guidance for the same indication.
	MS Society	We agree that NICE should appraise the clinical and cost effectiveness of ublituximab within its current or updated marketing authorisation for treating relapsing multiple sclerosis. We also agree that it is appropriate that NICE evaluate this technology through its Single Technology Appraisal process.	
	NHSE England	The proposed evaluation route seems reasonable. This does not represent a novel mechanism of action for this indication	
	Novartis Pharmaceuticals UK Ltd	No comments to add.	
	ABN	We support the evaluation of Ublituximab as a STA for the management of active relapsing remitting MS with clinical or radiological evidence of activity.	

Section	Stakeholder	Comments [sic]	Action
	Neuraxpharm UK Ltd.	We agree with NICE's suggestion that to adopt a cost-comparison approach for evaluating ublituximab, given the evidence indicating that it shows similar efficacy and safety as those anti-CD20 monoclonal antibody (mAb) therapies already recommended by NICE for the treatment of relapsing forms of MS (e.g., ocrelizumab and ofatumumab). Our reasoning for this recommendation is explained below. An independent review and network meta-analysis conducted by Samjoo et al. in 2023 showed that ublituximab is as clinically effective as other NICE-recommended mAb therapies, such as ofatumumab, natalizumab, alemtuzumab, and ocrelizumab. Ublituximab shows similarity in terms of annualised relapse rate (ARR) and confirmed disability progression at both 3 and 6 months (3mCDP and 6mCDP). Notably, mAb therapies, including alemtuzumab, natalizumab, ocrelizumab, ofatumumab, and ublituximab, stand out for their effectiveness in reducing ARR. Among these, alemtuzumab, ofatumumab, and ublituximab exhibit the most pronounced efficacy compared to placebo, with relative risks ranging from 0.28 to 0.31. Similarly, in terms of 3mCDP and 6mCDP, these mAb therapies, along with ponesimod and cladribine, emerge as the most effective options compared to placebo, as indicated by Hazard Ratios ranging from 0.39 to 0.59 and 0.41 to 0.54, respectively. Our recent (currently unpublished) systematic review and network meta-analysis confirm the findings of Samjoo et al. in 2023, reinforcing the strength of these conclusions. Moreover, data from the ULTIMATE I & II randomised clinical trials (Steinman et al., 2022) highlight ublituximab's efficacy in significantly reducing both ARR and the number of brain lesions seen on MRI when compared to teriflunomide over a span of 96 weeks. This evidence underscores the potential benefits of ublituximab for patients with RMS, a group for which teriflunomide is currently recommended.	

Section	Stakeholder	Comments [sic]	Action
		A cost-comparison case is most appropriate for ublituximab as it is likely to provide similar or greater health benefits at similar or lower cost than the mAbs recommended for in published NICE technology appraisal guidance for the RMS.	
Wording	Biogen Idec	Yes	Comments noted. No action required.
	MS Society	The wording of the remit reflects the issues of clinical and cost effectiveness that NICE should consider.	
	NHSE England	No challenges with the remit wording.	
	Novartis Pharmaceuticals UK Ltd	The wording is appropriate and accurate.	
	ABN	The remit provided is limited and both clinical and cost effectiveness about this TA are not part of this stakeholder comments document.	
	Neuraxpharm UK Ltd.	The wording in the remit is correct, but changes to the “Background” section have been suggested below. Please update wording to reflect MHRA-approved label on all documents for the Scoping exercise.	Comment noted. Scope updated to reflect MHRA-approved label.
	MS Society	None	Comments noted. No

Section	Stakeholder	Comments [sic]	Action
	Novartis Pharmaceuticals UK Ltd	No additional comments.	action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Biogen Idec	No comment	No action required.
	MS Society	The background information is accurate and complete.	
	NHSE England	The background information is incredibly brief but accurate. It does not cover the definitions or diagnostic criteria of MS, or the changes to this which have occurred since previous treatments were reviewed by NICE. The NICE approved treatment list is missing some options including ofatumumab.	Comment noted. Treatment options have been reviewed and updated to reflect current NICE approved treatments.
	Novartis Pharmaceuticals UK Ltd	The wording describing the ofatumumab NICE recommendation is not accurate. Please could the wording be updated to reflect the NICE recommendation from TA699; “Ofatumumab for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features.”	Comment noted. Wording of ofatumumab changed to reflect NICE recommendation TA699.
	ABN	The background is accurate	Response noted.
	Neuraxpharm UK Ltd.	In the “Background” section of the draft scope, we request the following change to the wording to be considered for accuracy and completeness:	Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		• 4th paragraph should outline the current positioning of mAb treatments as they target the immune system with high efficacy and specificity, which plays a key role in the early inflammatory stages of MS. • The scope document refers to alemtuzumab for active relapsing-remitting multiple sclerosis (NICE TA312), which should be corrected to specify alemtuzumab for highly active relapsing-remitting multiple sclerosis.	The background section of the scope aims to provide a brief summary of the disease and how it is managed and is not designed to be exhaustive. Scope has been updated to reflect wording in TA312.
Population	Biogen Idec	The population should be defined as adults with relapsing forms of multiple sclerosis aligned with the marketing authorisation	Comment noted. Scope has been updated to reflect marketing authorisation wording.
	MS Society	The population is defined appropriately.	Response noted.
	NHSE England	Yes, although clarity around how this fits with definitions used in previously appraised treatments is not provided.	Comment noted.
	Novartis Pharmaceuticals UK Ltd	The text would be more accurate if it stated ‘Adults with active relapsing-remitting multiple sclerosis.’	Comment noted. Scope has been updated to reflect marketing authorisation wording.
	ABN	The population is defined appropriately	Response noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Neuraxpharm UK Ltd.	The current population wording (RRMS) is not quite accurate as ublituximab has already been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for treating RMS patients (indication wording “adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features”).	Comment noted. Scope has been updated to reflect marketing authorisation wording.
Subgroups	Biogen Idec	No comment	Response noted
	MS Society	We agree that the suggested subgroups of people should be considered, if the evidence allows.	Comment noted. No action required.
	NHSE England	The sub groups are not in line with the comparators. It would be most appropriate to define the sub groups in line with the NHSE algorithm defined subgroups.	Comment noted. Scope has been updated so subgroups are in line with comparators and to reflect NHSE algorithm.
	Novartis Pharmaceuticals UK Ltd	Please could it be clear that the subgroups will include relapsing-remitting multiple sclerosis patients only as this is the licenced indication for ublituximab both EU and UK. Ublituximab is not licensed for ‘people with active secondary progressive multiple sclerosis’. We understand NICE guidance will only be issued in accordance with the UK marketing authorisation.	Comment noted. Scope has been updated to include relapsing-remitting multiple sclerosis as a subgroup and active secondary progressive multiple sclerosis has been removed.
	ABN	• People who have an intolerance to first line treatment • People who have disease activity on first line treatment	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• People who have disease activity on second line treatment • People with active secondary progressive multiple sclerosis All these are appropriate indications.	
	Neuraxpharm UK Ltd.	It is important to reconsider the way subgroups are delineated in the comparator sections for a few reasons. 1. Conducting a robust indirect treatment comparison analysis for the introduced subgroups is challenging. Previous trials have not consistently reported clinical efficacy based on treatment lines or on patients who exhibited intolerance to initial treatments. Therefore, achieving reliable data for such subgroup analyses would be exceedingly challenging, resulting in a lack of robust indirect treatment comparison results. 2. The majority of treatments recommended by NICE are applicable across various lines of treatment, including first, second, and third lines, as outlined in the NHS England Reference: 170079ALG - Updated: 20 June 2023. We expect the same to apply to ublituximab following its approval by NICE, according to the clinical advisory board. 3. Patients have been categorised into two groups in the comparators section: active and highly active RRMS, and rapidly evolving severe RRMS. However, it is unclear which classification should be the primary basis for subgroup analyses. Given these considerations, we recommend aligning with the final scope document for TA699 and preceding NICE Appraisals (TAs) for RRMS. Specifically, we propose revising the classification of subgroups to include:	Comments noted. Subgroups updated in line with comparators and to reflect NHS England treatment algorithm for multiple sclerosis.

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		1. Active and Highly active RRMS, and 2. Rapidly evolving severe RRMS. This adjustment would ensure consistency with established guidelines and facilitate more meaningful comparisons and evaluations in the assessment of ublituximab's efficacy and suitability for different patient populations.	
Comparators	Biogen Idec	The comparators listed will depend on the specific patient population / subgroup being considered as the NICE recommendations for each vary. Biogen suggest maintaining consistency with prior appraisal in RRMS or RMS. For example: treating active relapsing-remitting multiple sclerosis that is not highly active or rapidly evolving severe multiple sclerosis Dimethyl fumarate Diroximel fumarate Beta interferon Glatiramer acetate Teriflunomide Ocrelizumab Ofatumumab Ponesimod RES	Comments noted. Comparators have been updated to reflect relapsing MS population. This has been routed as a cost comparison evaluation and the comparators have been limited to ocrelizumab and ofatumumab.

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		Natalizumab Natalizumab Biosimilar Alemtuzumab Ocrelizumab Ofatumumab Ponesimod Cladribine tablets <u>Highly active disease despite a full and adequate course of a DMT</u> Fingolimod Generic Fingolimod Alemtuzumab Ocrelizumab Ofatumumab Ponesimod Cladribine Tablets The clinical and patient benefits of each of the potential comparators listed vary and so they should not be considered as a homogenous group.	
	MS Society	The listed comparators are considered the standard NICE approved treatments used in the NHS, and all relevant NICE approved comparators have been included.	Comments noted. No action required.

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		In addition, autologous haematopoietic stem cell transplantation is sometimes provided by the NHS as a DMT for select patients with active relapsing MS.	
	NHSE England	The comparators are appropriate, all relevant comparators are listed. As above there is discrepancy in the subgroups defined.	Comment noted. Comparators have been updated to reflect subgroups.
	Novartis Pharmaceuticals UK Ltd	No comments to add.	Comments noted. No action required.
	ABN	Yes they have been included	
	Neuraxpharm UK Ltd.	Based on the outlined evidence regarding the comparative efficacy of ublituximab against other NICE-recommended mAbs and teriflunomide, an approach focusing on cost-comparison appears to be the most efficient pathway for this evaluation. Therefore, the final scope should restrict comparators to only those anti-CD20 monoclonal antibody (mAb) therapies already recommended by NICE for the treatment of relapsing forms of MS (e.g., ocrelizumab and ofatumumab), alongside teriflunomide as products in the same drug class are eligible for consideration in the cost-comparison methodology. The inclusion of additional comparators would likely extend the evaluation period without offering significant added value, given the established efficacy of mAbs compared to other NICE-recommended treatments. Considering the latest network meta-analysis which positions ublituximab within the top three most effective treatments for multiple sclerosis, any	Comments noted. The comparators have been limited to ocrelizumab and ofatumumab.

Section	Consultee/ Commentator	Comments [sic]	Action
		process aimed at accelerating patient access to this medication could be immensely beneficial from a patient standpoint and result in the efficient utilisation of NHS resources.	
Outcomes	Biogen Idec	No comment	Response noted.
	MS Society	In addition to the outcomes listed, we would also suggest measures which go beyond largely physical measures of disability, such as EDSS score, to assess the impact of the technology on people's ability to remain in work, live independently and engage with family life. We recognise these outcomes can be hard to capture, but further engagement with patients and patient organisations can help to assess these impacts.	Comment noted. The list of outcomes is not exhaustive, therefore data on outcomes could be submitted, if available.
	NHSE England	The outcomes appear appropriate, although clarity on how relapse severity is to be measured would be useful.	Comment noted. No action required.
	Novartis Pharmaceuticals UK Ltd	'Relapse rate' is routinely presented as 'annualised relapse rate'. For 'disease progression', PIRA (progression independent or relapses) is now regarded as a critical measure for disease modifying therapies as this indicates whether a treatment is impacting the underlying processes as well as the inflammatory (relapse associated) activity. For 'freedom from disease activity', no evidence of disease activity (NEDA) is often assessed for overall efficacy and B-cell therapies are expected to provide high rates of NEDA.	Comment noted. The list of outcomes is not exhaustive, therefore data on those outcomes could be submitted, if available.

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		'Brain volume loss' is widely used as a robust outcome indicator in recent trials, as it provides a reliable comparison of neuroprotective potential of disease modifying therapies, we therefore suggest this is included as an outcome. Considering ublituximab is a new anti CD20, it is important to consider IgG and IgM levels as part of the safety outcomes. Decline in IgG and IgM levels have been associated with this class of drugs. In addition, the associated risk of infection must be taken into consideration for anti CD20s.	
	ABN	Yes appropriate outcomes have been included	Comments noted. No action required.
	Neuraxpharm UK Ltd.	The specified outcomes are fine.	
Equality	Biogen Idec	No Comment	Comments noted.
	MS Society	None	
	NHSE England	The MS population includes a proportion of females of childbearing age. The impact of disease modifying therapy on pregnancy outcomes is a factor which can mean that restrictions on access can more heavily impact the treatment choices for this patient group.	Comment noted. This will be considered by the committee.
	Novartis Pharmaceuticals UK Ltd	No comments to add.	Comments noted. No action required.
	ABN	We have identified no issues related to equality or discrimination of the MS population under consideration in the draft remit.	

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	Neuraxpharm UK Ltd.	None anticipated.	
Other considerations	Biogen Idec	We feel that a cost comparison is unlikely to be appropriate given the number of different comparators with efficacy/safety profiles and likely resource use (e.g. route & frequency of administration)	Comment noted. No action required.
	MS Society	None	Comments noted. No action required.
	NHSE England	Nil to add	
	Novartis Pharmaceuticals UK Ltd	No comments to add.	
Questions for consultation	Biogen Idec	No comments	Responses noted.
	MS Society	None	
	NHSE England	We would expect ublituximab to fit into the existing care pathway in line with already available anti-CD20 treatments. Managed access would be unlikely to be appropriate. Ublituximab would be expected to be similar to already available anti-CD20 treatments including ocrelizumab and ofatumumab	Comments noted. No action required.

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	Novartis Pharmaceuticals UK Ltd	Relating to the third question; ublituximab may offer patients with relapsing-remitting multiple sclerosis an additional treatment option. However the 'in clinic infusion' may add additional burden on the NHS. Considering that there were only two trial sites in the UK with a small number of patients, the generalisability of the data in reference to the overall UK population will need to be assessed.	Thank you for your comments.
	Neuraxpharm UK Ltd.	Q: Where do you consider ublituximab will fit into the existing care pathway for relapsing-remitting multiple sclerosis (see NHS England treatment algorithm)? A: Ublituximab should be considered an alternative to other disease-modifying therapy (DMT) mAbs per its MHRA-approved label. According to our recent clinical advisory board, ublituximab can be used at all lines of therapy, similar to the use of ofatumumab. Q: Would ublituximab be a candidate for managed access? A: We do not believe that a managed access scheme is appropriate as efficacy/safety data are similar to mAbs currently in use, so additional data collection is not required prior to access. Q: Do you consider that the use of ublituximab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? A: Indirect benefits of reduced infusion times and reduced monitoring after 3rd infusion may include improved patient quality of life which may not be captured in the QALY calculation due to lack of data. Q: Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		A: See SmPC for reduced infusion time and monitoring. Q: Please provide comments on the appropriateness of appraising this topic through this (cost-comparison) process. A: A cost-comparison case should be made for ublituximab as there is evidence pointing to a similar or greater health benefits (see Section Appropriateness of an evaluation and proposed evaluation route) it is likely to provide similar or greater health benefits (per NMA results) at similar or lower cost than the mAbs recommended for in published NICE technology appraisal guidance for the RMS. Q: Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators? A: Please see response in “Timing Issues” section. Q: Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe. A: According to the recently held clinical advisory board, ublituximab can be used at all three lines of therapy, similar to the use of ofatumumab. There have been no recent	

		changes in the treatment algorithm since last update September 2023. Q: Will the intervention be used to treat the same population as the comparator(s)? A: Yes, per the MHRA-approved label (see SmPC) Q: Overall, in the technology likely to offer similar or improved health benefits compared with the comparators? A: Please see response in “Timing Issues” section. Q: Would it be appropriate to use the cost-comparison methodology for this topic? A: We agree with NICE that a cost-comparison methodology should be considered for this topic on the premise that ublituximab offers similar or improved health benefits vs. anti-CD20 mAb therapies included in the recently unpublished SLR and NMA which will be used to support the NICE submission, whilst also potentially reducing costs of delivery due to its shorter infusion duration and less need for post-infusion monitoring. Ublituximab is the same class as ocrelizumab and ofatumumab and targets the same protein (CD20) as the mAbs currently used in NHS practice. It is intended that ublituximab will be used in the same patient population and place in therapy. It is administered via the same IV route as most other mAbs. Furthermore, considering that NICE has previously utilised a cost-comparison method for diroximel fumarate for RRMS, based on its comparator diroximel fumarate working in the same way and it being likely to be used in the same population.	

Section	Consultee/ Commentator	Comments [sic]	Action
		We firmly believe that ublituximab demonstrates an efficacy that is comparable to that of other anti-CD20 mAbs and teriflunomide, which NICE has already recommended. Consequently, a cost- comparison approach appears to be the most efficient route for this evaluation.	
	MS Society	None	Response noted.
	Novartis Pharmaceuticals UK Ltd	Regarding the Related National Policy; NHS England (2019) Treatment Algorithm for Multiple Sclerosis: Disease-Modifying Therapies. There has been an update in 2023.	Thank you for your comment. This has been updated.
	ABN	For a complex disease like MS, having additional treatment options for people to consider is incredibly important. Having a twice yearly infusion schedule with only an hours infusion is likely to also impact service considerations very positively.	Thank you for your comment.

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

Sanofi