National Institute for Health and Care Excellence

Health Technology Evaluation

Cladribine for treating relapsing multiple sclerosis

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	Merck Serono	This is considered to be appropriate.	Thank you for your comment. No action needed.
	Biogen Idec	Appropriate	Thank you for your comment. No action needed.
	The MS Society	We agree that NICE should appraise the clinical and cost effectiveness of cladribine 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.	Thank you for your comment. No action needed.
Wording	Merck Serono	This is considered to be appropriate.	Thank you for your comment. No action needed.

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	Biogen Idec	See general comments below, Section 2. Clearer statement re marketing authorisation (expected) for cladribine in relapsing MS (or relapsing remitting MS – RRMS).	Thank you for your comment. Your comments have been addressed below.
	The MS Society	The wording of the remit reflects the issues of clinical and cost effectiveness that NICE should consider.	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Merck Serono	The background information is considered accurate.	Thank you for your comment. No action needed.
	Biogen Idec	Where there is reference to alemtuzumab for active RRMS NICE should indicate when guidance TA312 will be updated. Where reference is made to treatment for active secondary progressive MS guidance for siponimod treatment is missing. See comments below on population and comparators, where more specific/clearer information is requested. Where the scope refers to the 'technology' it references that cladribine has been studied in a clinical trial in people with RRMS, please provide further information on this.	Thank you for your comment. The reference to the update to TA312 has been removed from the final scope as the TA312 recommendations were updated in line with the European Medicines Agency safety review outcomes in March 2020. The background section has been updated to include reference to NICE guidance

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			for siponimod for treating active secondary progressive multiple sclerosis (TA656). Comments on population and comparators have been addressed below. The technology section is intended to be a brief summary and is not an exhaustive description of the technology or the clinical trials in which is has been studied. No action needed.
	The MS Society	The background information is accurate and complete.	Thank you for your comment. No action needed.
	Multiple Sclerosis Trust	More could be said on the fact that each person with MS may need different treatments through their lifetime. Treatments that are appropriate during periods of high infection risk, through conception, pregnancy and breastfeeding, or during later life may not be appropriate at other times. For people with MS, having a range of options with varied mode of delivery and mode of action is essential for adequate disease management.	Thank you for your comment. The background section is intended to be a brief summary of the disease and treatment options. It is appreciated that different treatments may be appropriate

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			throughout an individual's lifetime, however this level of detail is not needed in the scope. No action needed.
Population	Merck Serono	Merck proposes that the population is defined more specifically as adults with active relapsing-remitting multiple sclerosis (RRMS) rather than adults with relapsing multiple sclerosis (RMS). This reflects the target population for reimbursement and will be aligned with the submitted evidence.	Thank you for your comment. The population section has been updated.
	Biogen Idec	Population is stated as 'Adults with relapsing MS', however greater clarity is requested on the specific population for this TA. Is the TA going to include HA RRMS? If so, is it the full population for HA RRMS (RES & SOT)? In section on 'population' there is reference to cladribine having already been evaluated for HARRMS, does this mean it is not in the scope of this proposed TA? The text in the background section indicates that HA RRMS is <u>not</u> going to be within scope of this TA, please be clearer in the final scope (e.g. for population and comparators).	Thank you for your comment. The population section has been updated to clarify that the population for whom cladribine has already been evaluated in TA616 (adults with highly active relapsing-remitting multiple sclerosis) will not be considered.
	The MS Society	The population is defined appropriately.	Thank you for your comment.
Subgroups	Merck Serono	No additional subgroups are suggested.	Thank you for your comment. The subgroup included in the scope may

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		It is requested that the subgroup 'people who could not tolerate previous treatment' is removed from the scope as Merck is not aware of any available data that indicates the relative effectiveness of DMTs will vary between patients who tolerate treatment and those who switch due to intolerance**.** A similar response was shared in recent MS appraisals regarding this subgroup (TA533, TA699, TA767) and was not considered in these appraisals due to lack of evidence.	be of clinical interest and so should be formally considered for evaluation. The scope specifies that the subgroup will be considered if the evidence allows. The availability (or lack) of evidence will be assessed during the evaluation. No action needed.
	The MS Society	We agree that the suggested subgroup of people who could not tolerate previous treatment should be considered, if the evidence allows.	Thank you for your comment. No action needed.
Comparators	Merck Serono	The patient population of interest is active RRMS and therefore it is considered that a comparison to rapidly evolving severe (RES) and secondary progressive multiple sclerosis (SPMS) are not appropriate for this evaluation. It is requested that the comparison for people with RES is removed from the scope, since the clinical and cost-effectiveness evidence for this sub-population has already been presented as part of the previous cladribine evaluation in highly active RRMS (TA616). No new evidence on this subgroup is available nor will it be submitted as part of this appraisal. It is also requested that the comparison for people with SPMS with evidence of active disease is removed from the scope, on the basis that the company does not intend to submit evidence or seek reimbursement in this patient population.	Thank you for your comment. It is acknowledged that people with rapidly evolving severe relapsing-remitting multiple sclerosis were considered in TA616. The comparators specific only to this population have been removed from the scope. The population of people with secondary progressive multiple sclerosis with evidence of active disease is considered appropriate and therefore comparators

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		Apart from the discrepancies aforementioned, the rest of the comparators section is considered appropriate.	specific for this population have remained in the scope.
	Biogen Idec	In list of stated comparators the scope refers to "optimised standard care with not disease modifying treatment", please provide further clarification on this. As question/request for 'Population', the stated comparators include treatments for RES, so further clarification is needed on whether RES (HA RRMS) is within scope or not? If not, remove stated RES treatments. If yes, full listing of appropriate comparators needed. For example, ocrelizumab, ponesimod, ofatumumab, optimised standard of care.	Thank you for your comment. Optimised standard care with no disease-modifying treatment refers to the care received when all other disease modifying active treatment options listed cannot be used. Comparators specifically only to people with rapidly evolving severe relapsing-remitting multiple sclerosis have been removed from the scope.
	The 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. In addition, autologous haematopoietic stem cell transplantation is sometimes provided by the NHS as a DMT for select patients with active relapsing MS.	Thank you for your comment. Autologous haematopoietic stem cell transplantation has been added to the scope as a comparator for people that progress on previous lines of treatment and after

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			discussion with a specialist multidisciplinary team.
Outcomes	Merck Serono	These are considered appropriate.	Thank you for your comment. No action needed.
	The MS Society	During the course of the appraisal, it will be important to consider the potential effects of the recommendations on the ability of people with MS to remain in work and engage with wider society, and the potential impact on carers. These outcomes can be difficult to capture with standard validated measures. However, they can be assessed through further engagement with patients and patient charities.	Thank you for your comment. The committee will consider if there are any uncaptured benefits from cladribine not included in the quality-adjusted life year calculation during the evaluation. No action needed.
Equality	Merck Serono	No changes are suggested.	Thank you for your comment. No action needed.
	The MS Society	In the event of a decision to expand the marketing authorisation for cladribine, the following equality considerations may apply to the NICE STA. MS affects two to three times as many women as men. Any NICE recommendation that resulted in fewer available treatment options for the wider population of people with active relapsing MS is likely to have a disproportionate effect on women. A decision by NICE not to recommend cladribine for the wider population of people with active relapsing MS may have a disproportionate impact	Thank you for your comment. The committee will consider all relevant equalities issues during the evaluation. These comments have been captured in the equality impact assessment. No action needed.

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		on younger people, who are more likely to consider family planning in their treatment decisions. Cladribine offers fewer restrictions on family planning compared to some other DMTs, as it involves treatment in years one and two with no further treatment after that. Both women and men can safely consider trying for a family after the six-month washout period following treatment.	
	Multiple Sclerosis Trust	The mode of delivery for cladribine means that it is particularly useful for some groups of people who often face discrimination and reduced access to health care. People who are insecurely housed or homeless, members of travelling communities such as Roma or Irish Travellers may benefit from expanded access to an effective treatment for RRMS that can be delivered over one week in a year, and with minimal monitoring. For people with lower incomes or disability that impacts on travel, this can impact their choice of disease modifying drug. We have heard from patients that the cost or accessibility of public transport to infusion clinics or prescribing hubs can mean that home-delivered DMDs are preferred to those given at hospital. This has led to people refusing highly effective treatments that require an expensive rail journey, time off work or assistance from carers, in favour of lower-efficacy treatments that they can deliver to themselves at home. Cladribine offers an effective option for treating these people with relapsing MS.	Thank you for your comment. The committee will consider all relevant equalities issues during the evaluation. These comments have been captured in the equality impact assessment. No action needed.

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Other considerations	Merck Serono	No further suggestions.	Thank you. No action needed.
	The MS Society	None	Thank you. No action needed.
	Multiple Sclerosis Trust	Patients currently have to fail on previous disease modifying therapy before being able to be offered cladribine, even if they and their prescribing neurologist regard it as a suitable choice. This leads to delay in reaching an effective treatment and potentially to the accumulation of irreversible disability in the meantime.	Thank you for your comment. No action needed.
Questions for consultation	Merck Serono	Where do you consider cladribine will fit into the existing care pathway for relapsing-remitting multiple sclerosis? Cladribine tablets will be positioned as a high-efficacy DMT for patients with active RRMS, regardless of line of therapy. Would cladribine be a candidate for managed access? No, cladribine will not be a candidate for managed access, given the quantity and quality of data available for cladribine and relevant comparators in RRMS. Any uncertainty that arises in this particular appraisal is not expected to be resolved by a period of managed access/data collection. Do you consider that the use of cladribine can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?	Thank you for your comment. No action needed.

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		Use of cladribine incurs benefits to patients associated with the oral administration method, as well as a reduced burden to the NHS. These benefits have been realised since the launch of cladribine in 2017, as discussed in the Time and Motion Study (Rog *et al.*, 2022(1), 2022(2))[1,2] 1. Rog, D *et al.* Understanding the administration and monitoring time burden of several disease-modifying therapies for relapsing multiple sclerosis, *Journal of Neurology, Neurosurgery & Psychiatry* 2022;93:e2 2. Rog, D *et al.* (2022) Understanding the administration and monitoring time burden of several disease-modifying therapies for relapsing multiple sclerosis (poster), MS Trust 2022 conference. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Data to be submitted will include randomised controlled trial data (from CLARITY and CLARITY-EXT studies), as well as post-marketing authorisation clinical and safety data, and real-world data.	
Additional comments on the draft scope	Merck Serono	None	Thank you. No action needed.
	Biogen Idec	Greater clarity needed on background, population and comparators.	Thank you for your comment. Your comments on the background, population and comparators have been addressed above.

Section	Consultee/ Commentator	Comments [sic]	Action
	Multiple Sclerosis Trust	This evaluation has the potential to resolve an anomaly in the MS treatment landscape.	Thank you for your comment. No action needed.

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

Sanofi