Review proposal of the definition of rapidly evolving severe multiple sclerosis in the recommendation wording of TA616 cladribine for treating relapsing–remitting multiple sclerosis

Rationale for change

1. Rapidly evolving severe multiple sclerosis (RES) is defined in the [TA616](https://www.nice.org.uk/guidance/ta616) cladribine guidance (published in 2019) as 2 relapses in the previous year and 1 T1 gadolinium-enhancing lesion at baseline MRI or a significant increase in T2‑lesion load compared with a previous MRI.
2. The clinical community and company consider this criteria may be overly restrictive because the requirement for 2 MRI scans places significant burden on a limited diagnostic and monitoring resource (MRI).

Proposal options

1. This review aims to investigate implications of changing the recommendation wording through consultation with key stakeholders. There may be a range of potential options resulting from this review including:
   1. No change to the recommendation wording, termination of the review.
   2. An adjustment to the recommendation wording, that does not require further submission of evidence or analysis.
   3. A review of the clinical and/or cost effectiveness of cladribine using alternative definitions for RES.
   4. A review of all recommendations that recommend treatment for RES multiple sclerosis.

Summary of new evidence and implications for review

1. There is no new evidence presented by the company for this review apart from clinical feedback. In addition, because of the nature of this review, NICE has not reviewed any updated published literature evidence for cladribine at this time.

## Are there any existing or proposed changes to the marketing authorisation policies that would affect the existing guidance?

1. The [marketing authorisation](https://www.medicines.org.uk/emc/product/8435/smpc#about-medicine) indication for cladribine specifies it should be used “for treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features”. These are defined in section 5.1 of the summary of product characteristics as:

* patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other DMDs
* patients with 2 or more relapses in the previous year, whether on DMD treatment or not.

Therefore, the company do not consider that the current wording of TA616 reflects the definition of RES in the license. However, the clinical evidence considered in the appraisal considered the definition of RES to be “patients with ≥2 relapses in the prior year whether on treatment or not AND Patients with ≥1 T1Gd+ lesion”

## What were the uncertainties identified in the original guidance relating to the recommendation wording?

1. In the original guidance, the committee considered the evidence for cladribine in the RES subgroup used post-hoc analysis. It has been noted in previous appraisals and clinical discussions that there is uncertainty with predicting which people are likely to follow a RES disease course at the point of clinical decision-making, which is not reflected by post-hoc analysis.

The original guidance also noted that the categorisations in marketing authorisations are difficult to use in clinical practice because there is a spectrum of disease activity rather than rigidly defined stages, and no universally accepted definition of highly active disease.

The clinical experts in the original appraisal also considered that the increase in T2‑lesion numbers compared with a previous MRI are an important indicator of disease activity, and may be more important than the absolute number, which led to the original wording of the recommendation.

In addition, the company notes that changes to the [McDonald criteria](https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(17)30470-2/abstract) have highlighted the need for reducing diagnostic delays and time to patients receiving DMTs.

## Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

1. Both natalizumab (TA127) and alemtuzumab (TA312) recommend treatment for a subgroup of people with RES disease. The recommendation wording is similar, defined as “2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI”.

# Questions for consultation

* What is the most appropriate definition of RES multiple sclerosis? How can people with RES-MS effectively be diagnosed in clinical practice and has this changed since the original appraisal?
* Are there any comments comparators and outcomes listed in the table above and do they align with the [NHS England treatment algorithm](https://www.england.nhs.uk/publication/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies/)?
* What are the current resource constraints and other considerations with using MRI to identify patients with RES-MS?
* Are there any additional considerations or advances in ability to predict which populations will likely follow a RES course of the disease before confirmation with a second MRI?
* How would other definitions of RES-MS align with the clinical evidence for cladribine? Are there any other sources of evidence for use of cladribine in populations with other definitions for RES-MS?
* Is there any new published evidence for clinical effectiveness of cladribine that should be considered in the scope of this review?
* What proportion of people that are diagnosed with RES-MS fulfil each of the criteria listed in the recommendation wording? What is the most critical criteria for defining a RES population?
* What can be learnt from the clinical experience of prescribing cladribine during the COVID-19 pandemic as an option if MRI was not possible due to service impact of the pandemic?
* Would there be any reason not to apply potential changes to the definition of RES disease to natalizumab and alemtuzumab recommendations?

Equality issues

1. No equality issues were identified in the original appraisal.

# Proposal paper sign off

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Appendix 1

# Scope of review

Review proposals require a scope using the PICO framework to describe the analysis that would be required if an economic analysis was considered appropriate. Please comment on the suitability of the proposed scope below.

## The technology

1. Cladribine tablets (Mavenclad, Merck Serono) is an orally administered deaminase-resistant deoxyadenosine analogue that targets CD19-positive B cells, CD8-positive and CD4-positive T-cells thought to be an important role in multiple sclerosis.

## Table 1: PICO framework

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| --- | --- |
| **Intervention(s)** | Cladribine tablets |
| **Population(s)** | Adults with rapidly evolving severe relapsing-remitting multiple sclerosis |
| **Comparators** | For people with rapidly evolving severe relapsing-remitting multiple sclerosis:   * alemtuzumab * natalizumab |
| **Outcomes** | The outcome measures to be considered include:   * relapse rate * severity of relapse * disability (for example, expanded disability status scale [EDSS]) * disease progression * symptoms of multiple sclerosis (such as fatigue, cognition or visual disturbance) * freedom from disease activity (for example lesions on MRI scans) * mortality * adverse effects of treatment * health-related quality of life. |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.  If the technology is likely to provide similar or greater health benefits at similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology guidance for the same indication, a cost-comparison may be carried out.  The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.  Costs will be considered from an NHS and Personal Social Services perspective. |
| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. |
| **Related NICE recommendations** | **Related technology appraisals:**  [Diroximel fumarate for treating relapsing-remitting multiple sclerosis](https://www.nice.org.uk/guidance/ta794) (2022). NICE technology appraisals guidance 767.  [Ponesimod for treating relapsing multiple sclerosis](https://www.nice.org.uk/guidance/ta767) (2022). NICE technology appraisals guidance 767.  [Ofatumumab for treating relapsing multiple sclerosis](https://www.nice.org.uk/guidance/ta699) (2021). NICE technology appraisals guidance 699.  [Ozanimod for treating relapsing multiple sclerosis](https://www.nice.org.uk/guidance/ta706) (2021). NICE technology appraisals guidance TA706.  [Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis](https://www.nice.org.uk/guidance/ta624) (2020). NICE technology appraisal guidance 624.  [Cladribine tablets for treating relapsing–remitting multiple sclerosis](https://www.nice.org.uk/guidance/TA616) (2017). NICE technology appraisal guidance 616.  [Ocrelizumab for treating relapsing–remitting multiple sclerosis](https://www.nice.org.uk/guidance/TA533) (2018). NICE technology appraisal guidance 533.  [Beta interferons and glatiramer acetate for treating multiple sclerosis](https://www.nice.org.uk/guidance/TA527) (2018). NICE technology appraisal guidance 527.  [Dimethyl fumarate for treating relapsing-remitting multiple sclerosis](http://www.nice.org.uk/Guidance/TA320) (2014). NICE technology appraisal guidance 320.  [Alemtuzumab for treating relapsing–remitting multiple sclerosis](http://www.nice.org.uk/Guidance/TA312) (2014). NICE technology appraisal guidance 312.  [Teriflunomide for treating relapsing–remitting multiple sclerosis](http://www.nice.org.uk/Guidance/TA303) (2014). NICE technology appraisal guidance 303.  [Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis](http://www.nice.org.uk/Guidance/TA127) (2007). NICE technology appraisal guidance 127.  **Related technology appraisals in development:**  [Evobrutinib for treating relapsing multiple sclerosis](https://www.nice.org.uk/guidance/indevelopment/gid-ta11357) [ID6313] Publication date to be confirmed  [Cladribine for treating relapsing multiple sclerosis](https://www.nice.org.uk/guidance/indevelopment/gid-ta11293) [ID6263] Publication date to be confirmed  **Related NICE guidelines:**  [Multiple sclerosis in adults: management](https://www.nice.org.uk/guidance/ng220). (2022) NICE guideline [NG220]  **Related quality standards:**  [Multiple sclerosis (2016)](https://www.nice.org.uk/guidance/qs108). NICE quality standard 108. |
| **Related National Policy** | NHS England (2019) [Treatment Algorithm for Multiple Sclerosis: Disease-Modifying Therapies](https://www.england.nhs.uk/publication/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies/)  The NHS Long Term Plan (2019) [NHS Long Term Plan](https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/)  NHS England (2018) [NHS manual for prescribed specialist services (2018/2019)](https://www.england.nhs.uk/publication/manual-for-prescribed-specialised-services/) |