

# Cladribine for treating relapsing–remitting multiple sclerosis

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

# Contents

1 Recommendations .....	4
2 Information about cladribine .....	6
Marketing authorisation indication .....	6
Dosage in the marketing authorisation .....	6
Price.....	6
3 Committee discussion .....	7
Clinical need and patient perspective.....	7
Treatment pathway and comparators.....	7
Comparators .....	9
Direct clinical evidence.....	10
Indirect clinical evidence .....	12
Company's economic model.....	15
Natural history of the disease in subgroup analyses .....	15
Treatment effect.....	16
Waning of treatment effect .....	16
Treatment stopping rates .....	17
Restarting treatment after relapse .....	18
Health-state costs .....	18
Caregiver quality of life.....	19
Other factors .....	19
Cost-effectiveness results and conclusion .....	20
4 Implementation.....	22
5 Appraisal committee members and NICE project team .....	23
Appraisal committee members .....	23
NICE project team .....	23
Update Information .....	24

This guidance replaces TA493.

# 1 Recommendations

- 1.1 Cladribine is recommended as an option for treating highly active multiple sclerosis in adults, only if the person has:
- rapidly evolving severe relapsing–remitting multiple sclerosis, defined by 2 or more relapses in the previous year, and baseline MRI evidence of disease activity, or
  - relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity.
- 1.2 This recommendation is not intended to affect treatment with cladribine that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

## Why the committee made these recommendations

Highly active relapsing–remitting multiple sclerosis is currently treated with alemtuzumab, fingolimod or natalizumab. This appraisal focuses on 2 subgroups of people with highly active relapsing–remitting multiple sclerosis, that is, those with rapidly evolving severe disease and those with suboptimally treated relapsing–remitting multiple sclerosis (disease that has responded inadequately to disease-modifying therapy).

Clinical trial results show that cladribine tablets (hereafter referred to as cladribine) reduce relapses and slow the progression of disability compared with placebo for people with relapsing–remitting multiple sclerosis. The effectiveness of cladribine for treating rapidly evolving severe or suboptimally treated relapsing–remitting multiple sclerosis is not proven, but it is likely to be more effective than placebo.

Based on indirect analyses, there is not enough evidence to determine whether cladribine is more or less effective than other treatments for people with rapidly evolving severe and

suboptimally treated multiple sclerosis. Because of this, cladribine and alternative treatments are considered equally effective for this appraisal.

The MRI criteria used by clinicians to define rapidly evolving severe relapsing–remitting multiple sclerosis have changed over time. In addition to the presence of T1 gadolinium-enhancing lesions at baseline, clinicians may now identify patients with rapidly evolving severe relapsing–remitting multiple sclerosis by a significant increase in T2-lesion load compared with a previous MRI.

Cladribine is less costly than other treatments and needs less frequent dosing and monitoring. It is cost effective compared with all other treatments, so can be recommended for rapidly evolving severe and suboptimally treated relapsing–remitting multiple sclerosis.

## 2 Information about cladribine

### Marketing authorisation indication

- 2.1 Cladribine tablets (Mavenclad, Merck Serono) are 'indicated for the treatment of adult patients with highly active relapsing multiple sclerosis as defined by clinical or imaging features'.

### Dosage in the marketing authorisation

- 2.2 In the summary of product characteristics, the recommended cumulative dose is 3.5 mg/kg body weight over 2 years, taken as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, 1 at the beginning of the first month and 1 at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 days or 5 days on which a patient takes 10 mg or 20 mg (1 or 2 tablets) as a single daily dose, depending on body weight. After completing the 2 treatment courses, no further cladribine treatment is needed in years 3 and 4.

### Price

- 2.3 The list price is £2,047.24 per 10 mg tablet (excluding VAT, BNF online, November 2019). Costs may vary in different settings because of negotiated procurement discounts.

## 3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Merck Serono and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

### Clinical need and patient perspective

#### Clinicians and patients would value an oral treatment with less frequent dosing and monitoring

- 3.1 Relapsing–remitting multiple sclerosis is a chronic, disabling neurological condition. The patient experts explained that relapses and residual disability between relapses can substantially reduce quality of life. The committee was aware that relapsing–remitting multiple sclerosis can limit people's ability to work, and to engage in social and family life. The patient experts also explained that many of the available treatments need frequent hospital appointments for treatment and monitoring and that this causes significant disruption to patients' lives and careers. The committee heard that an oral treatment taken in 2 short courses over 2 years would be less disruptive.

### Treatment pathway and comparators

#### The definitions of multiple sclerosis subgroups are not meaningful in NHS clinical practice

- 3.2 In the NHS, disease-modifying therapy is used to treat relapsing–remitting multiple sclerosis. The choice of therapy partly depends on the number of relapses and MRI evidence of disease activity, as defined in each treatment's marketing authorisation. Previous NICE technology appraisal guidance has usually defined active disease as at least 2 clinically significant relapses in the previous 2 years. The committee understood that some people with

relapsing–remitting multiple sclerosis have highly active disease but that there is no universally accepted definition of highly active disease. The company defined a group of people with 'high disease activity' as having either 1 relapse in the previous year while the person was on disease-modifying therapy and at least 1 T1 gadolinium-enhancing lesion on MRI, or at least 2 relapses (with or without lesions) in the previous year regardless of treatment. The clinical experts explained that this definition was not used in clinical practice and considered it to be very broad. The committee noted that, in previous appraisals, 'highly active disease' has been used to describe a population broadly similar to the population the company referred to as having suboptimally treated multiple sclerosis (see [section 3.3](#)). It also heard that, in practice, increases 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. The committee concluded that the group referred to by the company as having 'high disease activity' may not be meaningful in NHS clinical practice.

## **The subgroups in the company submission are appropriate for decision making**

3.3 People with 'high disease activity' relapsing–remitting multiple sclerosis were divided into 2 subgroups:

- Rapidly evolving severe relapsing–remitting multiple sclerosis: 2 or more relapses in the previous year whether the person was on treatment or not, and at least 1 T1 gadolinium-enhancing lesion.
- Suboptimally treated relapsing–remitting multiple sclerosis: at least 1 relapse in the previous year while the person was on disease-modifying therapy, and at least 1 T1 gadolinium-enhancing lesion or 9 T2 lesions.

In addition to these subgroups, the 'high disease activity' subgroup also included an undefined group of people, who the committee understood to be those with 2 or more relapses in the previous year without a T1 gadolinium-enhancing lesion. The clinical experts explained that this group was clinically identifiable, but that suboptimal treatment was more difficult to define. The committee considered that the suboptimal treatment subgroup represented people who have highly active disease that had responded inadequately to



previous treatment. However, it noted that the criteria used for MRI evidence of disease activity in this group may not be relevant for clinical practice, particularly given the concerns of the clinical experts about using the absolute number of T2 lesions as a criterion (see [section 3.2](#)). The clinical experts explained 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. However, they explained that the rapidly evolving severe and suboptimal treatment groups were broadly representative of patients at the more active end of the disease spectrum. The committee concluded that the subgroups broadly represent the population who would have cladribine tablets (hereafter referred to as cladribine) in clinical practice, and are appropriate for decision making. However, it also concluded that it would not use the company's definition of suboptimal treatment as the basis of any recommendation.

## Comparators

### The choice of comparator varies by subgroup

3.4 The clinical experts explained that many people with multiple sclerosis do not take disease-modifying therapies, but that people with highly active disease would. The committee understood that, for people with more active disease, clinicians follow NICE guidance, which recommends that people with rapidly evolving severe multiple sclerosis have alemtuzumab or natalizumab. Similarly, in line with NICE guidance, people with suboptimally treated multiple sclerosis (as defined in the company submission) could have alemtuzumab or fingolimod. The committee concluded that it was appropriate to consider the following comparators for cladribine:

- alemtuzumab and natalizumab for people with rapidly evolving severe disease
- alemtuzumab and fingolimod for people with suboptimally treated disease.

## Direct clinical evidence

### The main clinical evidence for cladribine comes from the CLARITY trial

- 3.5 The CLARITY trial was a randomised double-blind study of 1,326 people with active relapsing–remitting multiple sclerosis, which compared 2 different doses of cladribine with placebo. In the study, 433 people had the licensed dose (3.5 mg/kg body weight) of cladribine and 437 people had placebo. The primary outcome was annualised relapse rate. An important post-hoc outcome was time to 6-month confirmed disability progression.

### The relevant subgroups are defined post hoc in CLARITY

- 3.6 The company provided clinical evidence for the whole (intention-to-treat) population and for a post-hoc high disease activity subgroup from CLARITY. However, it did not provide cost-effectiveness estimates for these groups. The company's main evidence in its cost-effectiveness analysis was based on smaller post-hoc subgroups of the post-hoc high disease activity subgroup. These smaller subgroups were people with rapidly evolving severe and suboptimally treated relapsing–remitting multiple sclerosis. The company explained that it considered the rapidly evolving severe and suboptimal treatment post-hoc groups to broadly reflect the groups in previous NICE appraisals. The committee was concerned that the number of patients who had cladribine in these subgroups was small (50 and 19 patients respectively) meaning that the data based on these subgroups are uncertain. The committee agreed that evidence based on a larger pre-specified subgroup is preferable but appreciated that CLARITY had been planned before the current disease categorisations had emerged.

### Definitions of outcomes in CLARITY differ from other clinical trials and previous appraisals

- 3.7 To determine disability progression above the Expanded Disability Status Scale

(EDSS) state 5, a 0.5-point change in EDSS state was used in CLARITY, whereas other clinical trials used a 1.0-point change. A clinical expert explained that the difference between EDSS state 5 and EDSS state 5.5 is more subjective, and that it is less clinically significant than a change from EDSS state 5 to EDSS state 6, which requires the use of a walking aid. The committee noted that there were also differences in how a relapse was defined, with relapse-related disability specifically based on EDSS state in CLARITY but not in other trials. On balance, the committee considered that the differences in outcomes were unlikely to have a large effect on the comparative effectiveness, and concluded that the outcomes were broadly comparable across trials.

## Cladribine reduces relapses and delays disability compared with placebo in the whole population and the high disease activity subgroup

3.8 In the intention-to-treat analysis and in the high disease activity subgroup, cladribine reduced the annualised relapse rate and delayed disability progression sustained for 6 months compared with placebo (see table 1). The committee concluded that, for the overall population of people with relapsing–remitting multiple sclerosis and for the overall high disease activity subgroup, cladribine was more effective than placebo.

**Table 1 Results from CLARITY**

Outcome	Intention to treat (433 people having cladribine)	Overall high disease activity (140 people having cladribine)
Annualised relapse rate (rate ratio [95% confidence interval])	0.42 (0.33 to 0.53)	0.35 (0.24 to 0.50)
Time to confirmed 6-month disability progression (hazard ratio [95% confidence interval])	0.53 (0.36 to 0.78)	0.18 (0.08 to 0.44)

## Results for the rapidly evolving severe and suboptimal treatment subgroups are uncertain

3.9 In the rapidly evolving severe subgroup, cladribine reduced relapses and delayed disability progression compared with placebo. However, the effect on disability progression was not statistically significant. In the suboptimal treatment subgroup, the annualised relapse rate was lower with cladribine than with placebo, but the effect was not statistically significant. The effect on disability progression could not be estimated in this group because of small patient numbers. The exact results for the rapidly evolving severe and suboptimal treatment subgroups are commercial in confidence. The committee considered that the lack of statistical significance was partly because of the small patient numbers. It noted that, in the overall high disease activity group, which included both of the smaller subgroups, cladribine was highly effective and the results were statistically significant (see [section 3.8](#)). The committee concluded that, despite some uncertainty over the effect size, cladribine was likely to be more effective than placebo in both the rapidly evolving severe and suboptimal treatment groups.

## Indirect clinical evidence

### The company network meta-analysis is appropriate

3.10 The company's network meta-analysis compared cladribine with other treatments (including the comparators for this appraisal and other disease-modifying therapies such as beta interferon), in the overall population, and in the high disease activity, rapidly evolving severe and suboptimal treatment subgroups. The committee discussed the company's assumptions in the network meta-analysis:

- The company assumed that the relevant outcomes were comparable between trials, despite the differences in outcome measures in CLARITY compared with clinical trials for other treatments (see [section 3.7](#)). The ERG explained that it considered this to be a major limitation, but the company suggested that these subtle differences should not have a major impact. The committee agreed that the outcome measures used were broadly similar

across trials.

- The company assumed that the subgroups in CLARITY were comparable to those used in other clinical trials. The committee was aware that the definitions of high disease activity, rapidly evolving severe disease and suboptimally treated disease despite previous treatment differed from those used in previous NICE guidance for relapsing–remitting multiple sclerosis (see [section 3.2](#) and [section 3.3](#)). However, the committee considered that the subgroups were defined based on similar radiological and clinical criteria. It accepted that the subgroup populations were comparable between this appraisal and previously published appraisals.

The committee concluded that the network meta-analysis was appropriate for this appraisal.

## **The network meta-analysis does not provide conclusive evidence for the effectiveness of cladribine compared with current NHS treatments**

- 3.11 For each subgroup, the company used separate evidence networks to estimate the relative effectiveness of cladribine on annualised relapse rate, disability progression sustained for 3 months, and disability progression sustained for 6 months. Comparisons with cladribine were not possible for some of the comparators in each of the subgroups. Notably, results were not available for disability progression in the suboptimal treatment subgroup. Among the comparisons presented, cladribine did not have a statistically significant effect relative to its comparators (that is, alemtuzumab, fingolimod and natalizumab) on any of the outcomes in any of the subgroups. The committee also noted that the confidence intervals were wide and overlapped between treatments. It concluded that there was insufficient evidence from the network meta-analysis to show that cladribine had substantially different effectiveness to alemtuzumab, fingolimod or natalizumab.

## The meta-regression provides a full set of comparisons but may use invalid methods

3.12 The company did a meta-regression for the outcome of disability progression sustained for 6 months for cladribine, alemtuzumab, fingolimod and natalizumab compared with placebo to address the weaknesses of the network meta-analysis, particularly for the suboptimal treatment group. In the absence of data in the network meta-analysis (see [section 3.11](#)), the meta-regression estimated effectiveness based on differences in the baseline risk of disability progression. The committee noted that, although confidence intervals for cladribine, alemtuzumab, fingolimod and natalizumab compared with placebo were narrower than those for estimates in the network meta-analysis, they overlapped for all treatments in both the rapidly evolving severe and suboptimal treatment subgroups. It also noted that, for the rapidly evolving severe subgroup, the estimated effectiveness of cladribine compared with placebo from the meta-regression was similar to the estimate from the network meta-analysis. However, it was concerned that alemtuzumab compared with placebo appeared substantially less effective in the meta-regression than in the network meta-analysis. The company suggested this could be explained by the differences in baseline risk between trials. The company validated the methodology by comparing the effect sizes predicted by the meta-regression with the effect sizes seen in the relevant trials. The committee agreed with the ERG's concerns that there were differences in effect size not explained by differences in baseline risk, which would make the company's approach invalid. In addition, the committee was aware that the assumptions and issues which the network meta-analysis relied on (see [section 3.10](#)) also applied to the meta-regression. The committee acknowledged the company's attempts to address the data limitations, but on balance agreed that the meta-regression approach may be invalid. The committee concluded that, although the meta-regression did provide estimates for effect sizes adjusted for baseline risk, the evidence from the meta-regression was insufficient to show that cladribine had substantially different effectiveness to alemtuzumab, fingolimod and natalizumab.

## Company's economic model

### The model is appropriate for decision making

- 3.13 The committee noted that the company's model was similar to models used in previous NICE technology appraisal guidance, but that the company had removed progression to secondary progressive multiple sclerosis. The company explained that it was difficult to identify the transition to secondary progressive multiple sclerosis in clinical practice, and noted that health-related quality of life is more closely related to EDSS state than to the clinical form of multiple sclerosis. The company suggested that this meant that separating the 2 forms of the disease was unnecessary for economic modelling because all health-related benefits of treatment would be captured by changes in EDSS state. The committee concluded that the company's model was appropriate for decision making.

## Natural history of the disease in subgroup analyses

### Calculating different rates of disability progression in the subgroups is simplistic and potentially inaccurate

- 3.14 The natural history of multiple sclerosis in the company's economic model was based on the British Columbia multiple sclerosis dataset, which was used in previous NICE technology appraisal guidance. The company explained that the British Columbia dataset included a mixture of people with active and highly active multiple sclerosis. The company stated that rapidly evolving severe or suboptimally treated multiple sclerosis is expected to progress faster than active relapsing–remitting multiple sclerosis. Therefore, it adjusted the disease progression rates to allow for a higher probability of progression for EDSS states 0 to 6. This adjustment was based on the difference in 6-month confirmed disability progression in CLARITY in each subgroup compared with its complement (that is, people not included in that subgroup). The clinical experts and the ERG explained that, although assuming different rates of disease progression for each subgroup was reasonable, the company's approach was simplistic and potentially inaccurate. The committee appreciated that there was

no clear alternative data source or method, and was aware that such adjustment had not been used in previous technology appraisals. However, because the adjustment would have a limited effect on the cost effectiveness of cladribine, the committee did not pursue this point any further.

## Treatment effect

### **A scenario exploring equal clinical effectiveness should be considered in the economic analysis**

- 3.15 Because there was insufficient clinical evidence to show that cladribine had substantially different effectiveness to its comparators (see [section 3.12](#)), the ERG provided a scenario assuming that cladribine and its comparators were equally effective in reducing relapses and delaying disability progression. The committee concluded that, based on the evidence, it would take into account this ERG scenario in its decision making.

## Waning of treatment effect

### **The waning of the treatment effect should be the same for all comparators**

- 3.16 In previous NICE technology appraisal guidance for multiple sclerosis (such as for alemtuzumab and dimethyl fumarate), the committee agreed that most treatments for multiple sclerosis become less effective over time. Therefore, the economic modelling included the assumption that the treatment effect declines by 25% after 2 years and by 50% after 5 years for all therapies. The committee heard that the company had attempted to assess whether there was a declining effect of cladribine by analysing data from the extension of the CLARITY trial. The company used a treatment switching analysis to estimate a hazard ratio for disability progression for cladribine compared with placebo over 4 years. It showed that this hazard ratio was similar to the hazard ratio estimated over 2 years. Therefore, the company suggested that there was no evidence of the



treatment effect waning within the first 4 years. The company assumed that the waning effect for cladribine began after 4 years (that is, a 25% decline in treatment effect after 4 years and a 50% decline after 5 years). However, for the comparators, the company used the waning assumptions used in previous appraisals (that is, a 25% decline in treatment effect after 2 years and a 50% decline after 5 years). The committee noted that there was no statistically significant evidence to support different waning effects and that patient numbers used for the analysis in the subgroups were very small. It concluded that the company's evidence was insufficient to justify using a different treatment waning assumption for cladribine.

## Treatment stopping rates

### Applying annualised rates based on clinical trials is likely to overestimate treatment stopping rates

3.17 The company used the rates at which patients stop treatment with cladribine or its comparators from the respective clinical trials. The committee understood that, given the method of administration of both cladribine and alemtuzumab (that is, both involve 2 short courses of treatment a year apart), annual discontinuation rates did not apply, and the rate of stopping treatment refers to stopping between the first and second courses. The committee noted that fingolimod and natalizumab were all taken more frequently and for longer, so annual discontinuation rates were relevant. The ERG explained that people are more likely to stop treatment during the first year of treatment than in a subsequent year. Therefore, the company's approach of applying trial-based discontinuation rates to subsequent years would overestimate the number of people stopping treatment. In its exploratory analyses, the ERG assumed that, after the first 2 years of treatment, people only stopped treatment with fingolimod and natalizumab when there was no further clinical benefit (in the company model, until EDSS state 7, which would indicate secondary progressive multiple sclerosis). The committee concluded that the company had likely overestimated treatment stopping rates, but noted that this did not have a substantial effect on the cost-effectiveness analysis.

## Restarting treatment after relapse

### Restarting cladribine treatment should not be included in the economic model

- 3.18 The company included restarting treatment with cladribine and alemtuzumab following relapse in the economic model, which increased the costs but not the clinical effects of each treatment in the model. The ERG explained that there was no published effectiveness evidence on restarting treatment, and that it had removed this from the model in its exploratory analyses. The committee noted that cladribine's marketing authorisation does not refer to restarting treatment, and concluded that it should not be included in the economic model.

## Health-state costs

### Informal care costs should not be included in the model

- 3.19 The committee discussed the annual costs associated with each EDSS health state in the economic model. It noted that the company had used medical costs from Hawton and Green (2016) and non-medical costs from Karampampa et al. (2012), and that these were large compared with the health-state costs accepted in previous NICE technology appraisals. The committee noted that the company had included informal care costs. The ERG argued that these should be excluded to reflect the perspective of the NHS or personal social services on costs, as per the NICE reference case. In its exploratory analyses, the ERG used the UK MS Survey (using 2015/16 unit costs) as its source for EDSS state costs, which had been used in previous appraisals (including for dimethyl fumarate, fingolimod and natalizumab). The committee concluded that it was appropriate to exclude informal care costs and that the UK MS Survey values should be used for decision making.

## Caregiver quality of life

### **The effect on the quality of life of carers should be taken into account**

- 3.20 The ERG removed the quality-of-life decrement for carers of people with multiple sclerosis from the company's economic modelling because it considered this inconsistent with the NICE reference case. The committee was aware that previous NICE guidance for relapsing–remitting multiple sclerosis included utility values for caregivers. The committee agreed that it was important to recognise the impact that caring for people with multiple sclerosis has on caregivers, and concluded that caregiver quality-of-life decrements should be included in the cost-effectiveness analysis.

## Other factors

### **There is no evidence of any additional benefits of cladribine**

- 3.21 Cladribine is an oral treatment given in 2 short treatment periods over 2 years. The committee understood that this is significantly less disruptive to daily routines than existing treatments for multiple sclerosis, which need to be given more frequently or by injection. The committee agreed that these benefits would be welcomed by patients, and noted that existing oral treatments are all taken daily. However, the committee was not presented with evidence for the extent of these benefits in practice compared with other treatments. The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of quality-adjusted life years (QALYs).

## Cost-effectiveness results and conclusion

### The ERG's changes to the model are appropriate and are considered with the company's results

3.22 The committee had concluded that cladribine was clinically effective compared with placebo in the rapidly evolving severe and suboptimal treatment subgroups, but that there was insufficient evidence to determine whether cladribine was any more or less effective than its comparators (see [section 3.12](#)). The ERG had provided a scenario in which cladribine and its comparators (that is, alemtuzumab, fingolimod and natalizumab) were equally effective. The committee did not agree with the ERG's change excluding caregiver quality of life from the cost-effectiveness analysis (see [section 3.20](#)). The ERG also made other adjustments to the company's model:

- assuming equal waning of treatment effectiveness for cladribine and all comparators (see [section 3.16](#))
- assuming that after 2 years, trial discontinuation rates for fingolimod and natalizumab did not apply (see [section 3.17](#))
- removing restarting treatment with cladribine and alemtuzumab from the model (see [section 3.18](#))
- using EDSS health-state costs based on UK MS Survey data (see [section 3.19](#)).

The committee agreed that these changes were appropriate. It noted that the ERG had not explored the effect of some company assumptions, such as adjusting the natural history of disease progression (see [section 3.14](#)). However, it recognised that this was not likely to have a significant effect on cost effectiveness. The committee concluded that, although it did not fully reflect committee preferences, it would consider the ERG's exploratory scenario that assumes equal effectiveness of cladribine and its comparators in addition to the company base-case cost-effectiveness results.

### Cladribine is cost effective for rapidly evolving severe and

## suboptimally treated relapsing–remitting multiple sclerosis

3.23 In the company's base-case cost-effectiveness analysis, cladribine dominated (that is, was more effective and cheaper than) all other treatments. The committee noted that these results were based on effectiveness estimates from the company's meta-regression, which it had concluded was insufficient to show that cladribine had substantially different effectiveness from its comparators (see [section 3.12](#)). The committee therefore considered the effect of the ERG's exploratory analyses incorporating most of the committee's preferred assumptions and assuming equal effectiveness of cladribine, and the relevant comparators in both the rapidly evolving severe and suboptimal treatment subgroups. It noted that, in isolation, none of the ERG's changes to the company model changed the company's base-case results, and cladribine continued to dominate all other treatments in both subgroups. After combining the ERG's assumptions, cladribine remained more effective and cheaper than fingolimod and natalizumab in the relevant subgroups. Cladribine was less effective and cheaper than alemtuzumab in the combined scenario analysis in both the rapidly evolving severe and suboptimal treatment subgroups. This resulted in incremental cost-effectiveness ratios (ICERs) of £219,549 gained per QALY lost and £372,802 gained per QALY lost respectively. For interventions that are less costly and less effective than a comparator, an intervention is considered cost effective if the ICER generated is above the level considered acceptable rather than below it. The committee concluded that cladribine was a cost-effective use of NHS resources for rapidly evolving severe relapsing–remitting multiple sclerosis and suboptimally treated relapsing–remitting multiple sclerosis (that is, disease that has responded inadequately to disease-modifying therapy). However, the committee understood from the experts that it was not the number of, but the increase in, MRI lesions that is important to measure response to treatment (see [section 3.2](#)). It therefore agreed to refer to MRI evidence of disease activity rather than using the company's definition of suboptimal treatment.

## 4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh Ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that cladribine tablets are the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

## NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

### **Thomas Palmer**

Technical lead

### **Jasdeep Hayre**

Technical adviser

### **Jeremy Powell**

Project manager

## Update Information

**May 2024:** The wording in recommendation 1.1 has been updated to address concerns raised by the clinical community and company that the previously used definition of rapidly evolving severe multiple sclerosis (RES) was overly restrictive. This is because the requirement for 2 MRI scans places significant burden on a limited diagnostic and monitoring resource. The wording has now been changed to better reflect clinical practice.

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