NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Cladribine for treating active relapsing multiple sclerosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using cladribine in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: November 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using cladribine in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 09 January 2025
- Second evaluation committee meeting: 05 February 2025
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Cladribine is not recommended, within its marketing authorisation, for treating relapsing forms of multiple sclerosis with active disease, as defined by clinical and imaging features, in adults.

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.

NICE has separately evaluated cladribine for highly active multiple sclerosis in NICE's technology appraisal guidance on cladribine for treating relapsing–remitting multiple sclerosis.

Why committee made these recommendations

This appraisal evaluates cladribine only for active relapsing–remitting multiple sclerosis. This does not include everyone it is licensed for.

Disease-modifying therapies for active relapsing–remitting multiple sclerosis include dimethyl fumarate, diroximel fumarate, ocrelizumab, ofatumumab and ponesimod. The aim of treatment is to reduce the number of relapses, slow the progression of disability, and maintain or improve quality of life.

Clinical trial evidence shows that cladribine reduces the number of relapses and increases the time until disability progresses compared with placebo. Indirect comparisons suggest that the relapse rate with cladribine is lower than with beta interferons, glatiramer acetate or teriflunomide, and similar to that with dimethyl fumarate, ocrelizumab, ofatumumab and ponesimod. But the results of the indirect comparisons are uncertain because different trial designs and approaches were used in the included trials.

There are uncertainties in the economic evidence because the data used to model expected relapses and disability progression may not represent what happens in NHS clinical practice. Because of these uncertainties, it is not possible to determine the most likely cost-effectiveness estimates for cladribine for active relapsing–remitting multiple sclerosis. So, it is not recommended.

2 Information about cladribine

Marketing authorisation indication

2.1 Cladribine (Mavenclad, Merck Serono) is indicated for 'the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease as defined by clinical or imaging features'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cladribine.

Price

2.3 The list price is £2,047.24 per 10 mg tablet (excluding VAT, BNF online, November 2024). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The evaluation committee considered evidence submitted by Merck Serono, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Clinical need

3.1 Multiple sclerosis (MS) is a chronic, lifelong condition for which there is no cure. It causes progressive, irreversible disability, and many symptoms including pain, chronic fatigue, unsteady gait, muscle loss, speech

problems, incontinence, visual disturbance and cognitive impairment. Most people have the relapsing–remitting (RR) form of MS, which is characterised by periods of new or worsened symptoms. RRMS breaks down further into active, highly active and rapidly evolving severe forms. Over time, RRMS will progress to secondary progressive MS for most people which is characterised by progressive disability. For this appraisal, the committee evaluated cladribine only for people with active RRMS. This is because cladribine has already been evaluated for the highly active and rapidly evolving severe MS populations, and evidence for the secondary progressive MS population was not presented. The patient experts highlighted that RRMS is complex and unpredictable, and affects all aspects of life. They also explained that people with the condition have to plan extensively around their treatments. During the early stages of MS, people may find it difficult to care for their dependents or sustain their existing careers. In the later stages, they often need help from carers because of their accumulated disability. As MS progresses, it can worsen the quality of life for people with the condition and for their carers. The committee concluded that MS can have a substantial impact on quality of life.

Benefits of cladribine

3.2 Because MS is typically diagnosed when people are of child-bearing age, the patient experts highlighted the significance of a treatment, like cladribine, that may have fewer restrictions for family planning. They also highlighted that the low treatment administration and monitoring burden of cladribine offers particular benefit to people who:

- live far from specialist centres
- have insecure housing or are experiencing homelessness
- otherwise find it difficult to travel for treatment. The committee heard that an oral treatment taken in 2 short courses over 2 years would be less disruptive than some available treatments.

The company and clinical experts highlighted the long-acting effect of cladribine, which can delay relapses and the need for subsequent disease-modifying therapies. The committee concluded that cladribine's dosing schedule has benefits compared with existing treatment options.

Treatment pathway

Clinical management

3.3 In the NHS, disease-modifying therapies are used to treat RRMS. The aim of treatment is to reduce the number of relapses, slow the progression of disability, and maintain or improve quality of life. The choice of therapy partly depends on the number of relapses and evidence of disease activity, as defined in each treatment's marketing authorisation. The clinical experts explained that the NHS treatment algorithm for multiple sclerosis disease-modifying therapies informs prescribing decisions. As a treatment is found to be ineffective for someone, or relapse or disease progression occurs, they may switch to an alternative treatment. Non-pharmacological treatments, such as physiotherapy, are also used to manage the condition. The committee concluded that cladribine would be a welcome additional treatment option for people with MS.

Comparators

3.4 For people with active RRMS, the company submission compared cladribine with beta interferons, dimethyl fumarate, diroximel fumarate, glatiramer acetate, ocrelizumab, ofatumumab, ponesimod and teriflunomide. The clinical experts agreed that ocrelizumab, ofatumumab, and ponesimod are considered 'high-efficacy' disease-modifying therapies, and that these were the most relevant comparators for cladribine. They noted that prescribing varies, with input from healthcare

professionals and people with MS, to suit the needs and preferences of individuals. They added that, in NHS clinical practice:

- ocrelizumab and ofatumumab are the most commonly prescribed treatments for active RRMS
- ponesimod, dimethyl fumarate and diroximel fumarate may be used because they are taken orally
- glatiramer acetate and beta interferons are not routinely prescribed.

So, the committee concluded that the most appropriate comparators for cladribine were dimethyl fumarate, diroximel fumarate, ocrelizumab, ofatumumab and ponesimod.

Clinical evidence

Clinical-effectiveness data sources

3.5 The main clinical evidence for cladribine was from the CLARITY and CLARITY-EXT trials. CLARITY was a randomised double-blind study of 1,326 people with active and highly active RRMS. It compared 3.5 mg/kg and 5.25 mg/kg doses of cladribine with placebo. The lower dose of 3.5 mg/kg was used in the company submission. The primary outcome was qualifying annualised relapse rate (ARR). Other clinical outcomes included proportion of people who were relapse free, time to 3-month confirmed disability progression (CDP) and time to first qualifying relapse. Time to 6-month CDP was a post-hoc outcome. CLARITY-EXT was a 2-year extension study of CLARITY, in which the primary outcomes were safety and tolerability. Other secondary outcomes in CLARITY-EXT included qualifying ARR, time to first and second relapse, and time to 3-

month CDP. The committee concluded that CLARITY and CLARITY-EXT were generalisable to the NHS.

Clinical effectiveness

3.6 There was a statistically significant 58% reduction in ARR with 3.5 mg/kg cladribine tablets at 96 weeks compared with placebo (0.14 compared with 0.34; $p<0.0001$). There was also a statistically significant delay in the time to first qualifying relapse with 3.5 mg/kg cladribine tablets compared with placebo (hazard ratio 0.45, 95% confidence interval 0.34 to 0.58; $p<0.0001$). Also, the results showed that statistically significantly fewer people had 3-month CDP and statistically significantly more people remained relapse free at 96 weeks with 3.5 mg/kg cladribine tablets compared with placebo. The clinical experts found it hard to draw direct comparisons between treatments because of the lack of head-to-head trials with cladribine. But they said that in their experience cladribine offers sustained remission from symptoms for some people with highly active RRMS who take it. Their experience in clinical practice aligns with cladribine being an effective disease-modifying therapy with a good safety and tolerability profile. The patient experts described cladribine as being considerably easier for them to take and adhere to than other treatments. They added that it substantially improves quality of life because it helps them:

- avoid flareups when travelling to appointments
- remain in work
- better plan a family.

The committee concluded that cladribine leads to longer delays in time to qualifying relapse and a reduction in annualised relapse rates compared with placebo.

Network meta-analysis

3.7 Because there was no head-to-head evidence comparing cladribine with relevant comparators in the RRMS population, a network meta-analysis (NMA) was done for each outcome of interest for the whole RRMS population. The NMAs included 38 trials from between 1987 and 2022 and compared outcomes across cladribine and the comparator treatments in active RRMS. The company's NMAs were similar to NMAs done for previous NICE technology appraisals of treatment for RRMS, and produced comparable estimates to recent NICE technology appraisals in RRMS. Several randomised controlled trials contributed to the NMAs for each of the ARR (37 studies), 3-month CDP (15), 6-month CDP (17) and treatment discontinuation (25) sets of outcomes. The results were:

- There was a statistically significantly lower ARR with cladribine than with beta interferons, glatiramer acetate, placebo and teriflunomide. There was no statistically significant difference in ARR between cladribine and ocrelizumab, ofatumumab, dimethyl fumarate and ponesimod.
- There was a statistically significant reduction in CDP with cladribine than with placebo. Wide and overlapping credible intervals meant that there were no statistically significant differences between cladribine and other disease-modifying therapies in CPD.

- There was a statistically significantly lower risk of people stopping treatment with cladribine compared with interferon beta-1a (44 microgram). There were no statistically significant differences in treatment discontinuation between cladribine and the other disease-modifying therapies because of wide and overlapping credible intervals.

The company acknowledged that differences between study characteristics (diagnostic criteria, study phase, blinding), population (disease duration, treatment history) and outcomes definitions contributed to greater uncertainty in the results. This then challenged

the reliability of NMA estimates. The EAG explained that these differences were a limitation. It thought that this uncertainty likely could not be overcome and advised interpreting the NMA results with caution. The company tried to address these differences by showing that baseline risk-adjusted NMAs had similar results. The committee agreed that this may reduce the uncertainty associated with the NMA results, but it had not seen a direct comparison of results from this model. The committee acknowledged the uncertainty in the NMA results, noting that they were for the whole RRMS population, but concluded that the company's NMAs were sufficient for decision making. It welcomed comparison and best-fit assessment of adjusted and unadjusted NMAs.

Economic model

The company's model structure

3.8 The company's model was a Markov transition model consisting of 11 health states (10 Expanded Disability Status Scale [EDSS] states for relapsing forms of MS, and death). The EAG agreed with the company's preference for an 11-state model not including secondary progressive MS and simpler than models previously used in RRMS NICE technology appraisals. There were 2 key features to the model:

- a natural history reference model that modelled the baseline transitions of people with MS regardless of treatment
- a treatment-adjusted model that incorporated treatment effects for cladribine and all comparators from the company's NMAs.

The treatment effects were applied to adjust progression through each of the EDSS states using confirmed disability accumulation at 6 months. Relapses were modelled independently using ARR ratios from the NMAs. The committee noted that concerns have been raised about many of the assumptions made in the models used in previous NICE technology appraisals, including:

- the lack of treatment switching or sequencing
- the validity of the fixed waning assumptions
- the relevance of the source of mortality data to NHS clinical practice.

The committee concluded that the model structure and inputs broadly aligned with models used in previous technology appraisals on treatments for MS. But it thought that the model had considerable structural uncertainty.

Source of natural history data

3.9 The model used the British Columbia Multiple Sclerosis (BCMS) registry as a source of natural history data. This has been used in previous NICE technology appraisals on technologies for MS. The clinical experts explained that the BCMS registry data is not representative of the MS population in the NHS. They added that this is especially so for people whose RRMS is considered active and not highly active. They described that, in recent decades, treatment and care for people with MS has improved prognosis, so progression to more significant disability (higher EDSS states) is less common. The committee noted that the BCMS registry data for disability progression was collected between 1980 and 1995. It thought that the modelling of EDSS state transitions was implausible because of the high proportion of people in higher EDSS states. The clinical experts added that mortality events are less common than in the BCMS registry data. The clinical experts said that people with MS today have a mortality profile that is much closer to that of the general population than that of historical MS populations. Also, people with MS often die of causes not related to MS. The committee concluded that the company should have validated the natural history model with more recent data, such as from the UK MS registry, that:

- represents the active MS population in the NHS
- does not include data of people with highly active RRMS at baseline.

The committee agreed that it would also welcome validation for the existing BCMS registry data and support showing that it reflects outcomes for people with active RRMS in the NHS.

Treatment discontinuation probabilities

3.10 In the company's base case, annualised treatment discontinuation probabilities were derived from the NMA for comparators and drawn from CLARITY for cladribine. Treatment discontinuation probabilities varied for 0 to 1 years, 2 to 9 years, and 10 years and over. Because cladribine was administered in years 1 and 2, the only discontinuation modelled by the company for cladribine were between those years. The EAG thought that real-world evidence would be more generalisable to the NHS than an NMA of randomised controlled trials. So, it modelled treatment discontinuation using more recent real-world-evidence studies. Also, the EAG used a broader definition of treatment discontinuation, which considered overall treatment persistence. The EAG assumed that people stop treatment if they take a different disease-modifying therapy. So, if someone had 2 years of cladribine, then started taking a different treatment, this counted as cladribine discontinuation in the EAG's model, but not in the company's model. The EAG said treatment discontinuation had been underestimated for cladribine because people may switch to another disease-modifying therapy. But as it is currently modelled, the benefits would still be accrued for cladribine.

The committee agreed that switching to another treatment should be considered cladribine discontinuation. It noted that the lack of treatment sequencing was a limitation of the underlying model structure which presented difficulty given the modelled short administration and ongoing effect of cladribine. The clinical experts thought that the EAG's treatment discontinuation probabilities were an overestimate, and the company's probabilities were an underestimate. Also, they thought that the treatment waning aspect of the modelling, which captured a decline in the treatment

effect over time, was confounding. This was because people within their care would have a disease-modifying therapy for as long as it worked and then switch to another treatment. People would not stay on a partially effective treatment. The company and EAG were aligned on applying treatment waning. The clinical experts acknowledged that some people continue to get the full treatment benefit of the drug over a long time period. But added that other people experience progression or relapse. The committee concluded that neither the company's nor EAG's discontinuation probabilities reflected NHS practice. Rather, the committee would have liked to be able to consider time to next treatment. The committee suggested that the company use time to next treatment data from CLASSIC-MS, which has over 10 years of follow-up data. It recommended using this study for stopping cladribine and comparator treatments or, when not applicable, the company's NMA.

Mortality rates

3.11 In the company's base case, the same mortality rate was applied to people with MS, regardless of their level of disability (EDSS status). The EAG preferred to use mortality rates that differed by EDSS state. This was because using the same mortality rate for all EDSS states implied no survival advantage from slowing disease progression with disease-modifying therapies. The clinical experts explained that, with new treatments and improved care, mortality rates for people with MS have improved in recent years. They said people with MS now rarely die from MS. The committee concluded that people in higher EDSS states have a higher mortality risk than people in lower states. So, mortality rates should have varied by EDSS state. The committee was concerned that the current natural history model, which overpredicted occupation of the high EDSS states over time, would overpredict mortality using variable mortality rates. It requested graphs of health-state occupation to understand and appraise the model transitions. The committee was concerned that the data used to estimate the EDSS-specific rates from

Pokorski et al. 1997 was outdated and not generalisable to people with MS in the NHS. It concluded that more recent data, such as Harding et al. (2018), should be used to inform the mortality rates used for each EDSS state in the cost-effectiveness model. Justification and validation of mortality data should be provided to improve the generalisability of the model outputs to the NHS population.

Self-injection training for comparator treatments

3.12 The company's base case included 3 hours of nurse time to teach people to inject themselves with injectable disease-modifying therapies. The EAG said that this training is typically provided by company-sponsored nurses, so is not a cost to the NHS. The clinical experts confirmed that training was provided by company-sponsored nurses for ofatumumab. But they said that the companies did not provide training for older treatments (such as beta interferons) because people do not often start treatment with these anymore. The clinical experts noted that the support provided by company-funded nurses may stop in the future. The committee concluded that the model should have reflected current practice. So, the cost of injection device training for patients should not have been included.

Cladribine monitoring costs

3.13 The company's base case included lower monitoring costs for people taking cladribine than did the EAG base case. It included 1 MRI scan in the first year of treatment and 0 MRI scans in the second year of treatment. The EAG's base case included 1 MRI scan in both the first and second years of treatment. Also, the company's base case included 1 neurology appointment in the second year of treatment, while the EAGs base case included 2 appointments. The clinical experts said that people would typically have 1 MRI scan during the first 2 years of cladribine treatment (typically in the second year rather than the first year). They also said that people would have 1 neurology appointment each year. The committee preferred the company's approach of including 1 MRI scan and

2 neurology appointments in total for the 2-year period of active cladribine treatment.

Monitoring costs for glatiramer acetate and beta interferons

3.14 The company's base case included higher monitoring costs for people taking glatiramer acetate and beta interferons in the first year of treatment than the EAG's base case. The company's model included 2 neurology appointments, and the EAG's base case included 0 appointments. The clinical experts said that people would typically have 1 appointment in the first year when taking a disease-modifying therapy. The committee concluded that 1 neurology appointment should be included in the model. But glatiramer acetate and beta interferons were not considered to be relevant comparators, so may not be included in future analyses.

Cost effectiveness

The committee's preferred cost-effectiveness assumptions

3.15 The committee concluded that its preferred assumptions for the cost-effectiveness modelling of cladribine for active RRMS were to:

- use an updated data source for the natural history model to reflect the population with active RRMS in the NHS or validate the current BCMS registry data (see section 3.9)
- include the waning assumption agreed by the company and EAG (see section 3.10)
- use variable EDSS-specific mortality rates based on more recent data validated for the population with active RRMS in the UK (see section 3.11)
- use the EAG's assumption to exclude nurse-led self-administration costs for injectables because the analysis ought to reflect NHS clinical practice (see section 3.12)

- use 1 MRI scan and 2 neurology appointments across the first 2 years of cladribine to capture accurate monitoring costs in line with NHS clinical practice (see section 3.13)
- remove beta interferons and glatiramer acetate as comparators (see section 3.14).

Assessment of cost effectiveness

3.16 The relevance of the cost-effectiveness evidence to NHS clinical practice and structural aspects of the economic modelling were sources of uncertainty. Based on the uncertainty in the economic model, the committee was unable to determine the most likely cost-effectiveness estimates for cladribine in people with active RRMS. So, the committee requested further analyses from the company to address its outstanding concerns, including:

- new analysis that uses validated natural history data and EDSS transition probabilities for the population with active RRMS in the NHS (see section 3.9)
- data on time to next treatment from CLASSIC-MS for treatment discontinuation probabilities for cladribine and the comparator treatments or, when not available or applicable, use of the company's NMA (see section 3.10)
- subsequent treatment lines in the model to appropriately model time to next treatment (see section 3.10)
- more recent data, such as Harding et al. 2018, to inform the mortality rates used for each EDSS state in the cost-effectiveness model (see section 3.11)
- graphs showing health-state occupation that reflects EDSS state progression and mortality (see section 3.11).

Other factors

Equality

3.17 The committee heard that MS disproportionately affects women more than men. Also, it is diagnosed in younger people. The committee noted that the issue of different disease prevalence cannot be addressed in a technology appraisal. The committee also noted that MS has significant lifelong effects on family planning, employment and financial decision making. The burden of some treatments can be challenging for some, for example:

- people who have insecure housing or are experiencing homelessness
- members of the travelling community
- people who find travel more difficult such as people with lower incomes or disabled people.

The committee considered the benefits of cladribine; the low treatment administration and monitoring burden for these population groups and communities in its decision making.

Conclusion

Recommendation

3.18 The committee concluded that there were uncertainties in the clinical- and cost-effectiveness evidence. This meant that it was not possible to determine the most likely cost-effectiveness estimates or a maximum

acceptable incremental cost-effectiveness ratio for cladribine. So, the committee could not recommend cladribine for active RRMS in adults.

4 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Dr Charles Crawley
Chair, technology appraisal committee B

NICE project team

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

Alexandra Sampson and Sammy Shaw
Technical leads

Rufaro Kausi
Technical adviser

Kate Moore

Project manager

Lorna Dunning

Associate director

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