NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Cladribine for treating relapsing multiple sclerosis

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of cladribine within its marketing authorisation for treating relapsing multiple sclerosis.

Background

Multiple sclerosis is a chronic, neurological condition which affects the brain, optic nerves, and spinal cord. It often results in progressive neurological impairment and severe disability. Multiple sclerosis has an unpredictable course which varies in severity and rate of progression. Symptoms can include pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance, and cognitive impairment. Relapsing–remitting multiple sclerosis is the most common clinical form of multiple sclerosis. It is characterised by periods of remission (where people may have no symptoms, or they may be relatively stable) followed by relapses (which may or may not result in residual disability). Relapsing–remitting multiple sclerosis can progress to secondary progressive multiple sclerosis. This is characterised by more persistent or gradually increasing disability. Some people with secondary progressive disease continue to have relapses.

Over 130,000 people in the UK have multiple sclerosis, and about 7,000 people are diagnosed each year.[1] Approximately 85% of people are diagnosed with relapsing–remitting multiple sclerosis[2-3], and around 50% of people transition to secondary progressive multiple sclerosis within 20 years[4]. A small number of people are diagnosed with secondary progressive multiple sclerosis without a previous diagnosis of relapsing–remitting multiple sclerosis.

Current pharmacological management of multiple sclerosis includes disease-modifying agents to reduce the frequency and severity of relapses and the rate of disease progression.

NICE recommends the following treatment options for relapsing–remitting multiple sclerosis:

- diroximel fumarate for treating active relapsing-remitting multiple sclerosis that is not highly active or rapidly evolving severe multiple sclerosis (NICE TA794)
- ponesimod for treating active relapsing-remitting multiple sclerosis (NICE TA767)
- ofatumumab for treating active relapsing-remitting multiple sclerosis that is not highly active or rapidly evolving severe multiple sclerosis (NICE TA699)
- peginterferon beta-1a for treating relapsing-remitting multiple sclerosis (NICE TA624)
- cladribine tablets for treating highly active multiple sclerosis only for rapidly evolving severe relapsing–remitting disease or disease that has responded inadequately to treatment with disease-modifying therapy (NICE TA616).

- ocrelizumab for active relapsing–remitting multiple sclerosis only if alemtuzumab is contraindicated or otherwise unsuitable (NICE TA533)
- interferon beta-1a and glatiramer acetate for relapsing–remitting multiple sclerosis and interferon beta-1b for relapsing–remitting multiple sclerosis with 2 or more relapses within the last 2 years (NICE TA527)
- teriflunomide and dimethyl fumarate for active relapsing–remitting multiple sclerosis, only if people do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis (NICE TA303 and TA320 respectively)
- alemtuzumab for active relapsing–remitting multiple sclerosis (NICE TA312[a])
- fingolimod for highly active relapsing–remitting multiple sclerosis in adults who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon (NICE TA254)
- natalizumab for rapidly evolving severe relapsing–remitting multiple sclerosis (NICE TA127)

Treatments for relapsing–remitting multiple sclerosis are also used for people with active secondary progressive multiple sclerosis, as evidenced by relapses. NICE TA527 recommends interferon beta-1b for treating secondary progressive multiple sclerosis in people with continuing relapses.

The technology

Cladribine (Mavenclad, Merck Serono) does have a marketing authorisation in the UK for the treatment of adult patients with highly active relapsing multiple sclerosis as defined by clinical or imaging features. However, it does not currently have a marketing authorisation in the UK for the treatment of the broader population of adults with active relapsing multiple sclerosis. It has been studied in a clinical trial compared to placebo in people with relapsing-remitting multiple sclerosis.

Intervention	Cladribine
Population	Adults with relapsing multiple sclerosis. Cladribine has already been evaluated for adults with highly active relapsing multiple sclerosis.
Subgroups	If the evidence allows, the following subgroup of people will be considered: • people who could not tolerate previous treatment.

[a] In October 2019, the European Medicines Agency's pharmacovigilance risk assessment committee recommended restricting alemtuzumab to use in adults with relapsing remitting multiple sclerosis that is highly active despite adequate treatment with at least one disease-modifying therapy or if the disease is worsening rapidly with at least two disabling relapses in a year and brain-imaging showing new damage. The recommendations in NICE TA312 will be updated to reflect this in due course.

Comparators	For people with active relapsing multiple sclerosis: • beta interferon • dimethyl fumarate • diroximel fumarate • glatiramer acetate • teriflunomide • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • peginterferon beta-1a • ofatumumab • ponesimod • optimised standard care with no disease-modifying treatment In addition, for people with rapidly evolving severe relapsing-remitting multiple sclerosis: • alemtuzumab • natalizumab For people with secondary progressive multiple sclerosis with evidence of active disease: • siponimod • beta-interferon
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. 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 (2022). NICE technology appraisals guidance 767. Ponesimod for treating relapsing multiple sclerosis (2022). NICE technology appraisals guidance 767. Ofatumumab for treating relapsing multiple sclerosis (2021). NICE technology appraisals guidance 699. Ozanimod for treating relapsing multiple sclerosis (2021). NICE technology appraisals guidance TA706. Siponimod for treating secondary progressive multiple sclerosis (2020). NICE technology appraisal guidance 656. Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (2020). NICE technology appraisal guidance 624. Cladribine tablets for treating relapsing–remitting multiple sclerosis (2017). NICE technology appraisal guidance 616. Ocrelizumab for treating relapsing–remitting multiple sclerosis (2018). NICE technology appraisal guidance 533. Beta interferons and glatiramer acetate for treating multiple sclerosis (2018). NICE technology appraisal guidance 527. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (2014). NICE technology appraisal guidance 320. Alemtuzumab for treating relapsing–remitting multiple sclerosis (2014). NICE technology appraisal guidance 312. Teriflunomide for treating relapsing–remitting multiple sclerosis (2014). NICE technology appraisal guidance 303.

	Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (2007). NICE technology appraisal guidance 127. **Related NICE guidelines:** Multiple sclerosis in adults: management (2022). NICE guideline 220. **Related interventional procedures:** Percutaneous venoplasty for chronic cerebrospinal venous insufficiency in multiple sclerosis (2019). NICE interventional procedure guidance 640. **Related quality standards:** Multiple sclerosis (2016). NICE quality standard 108.
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2019) Treatment Algorithm for Multiple Sclerosis: Disease-Modifying Therapies NHS England (2018) NHS manual for prescribed specialist services (2018/2019)

Questions for consultation

Where do you consider cladribine will fit into the existing care pathway for relapsing-remitting multiple sclerosis?

Would cladribine be a candidate for managed access?

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?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which cladribine will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

References

1. Multiple Sclerosis Society MS in the UK [accessed June 2023].

2. Multiple Sclerosis Society (2019) Relapsing remitting MS (RRMS) [accessed June 2023].

3. MS International Federation (2022) Types of MS [accessed June 2023].

4. Barzegar M, Najdaghi S, Afshari-Safavi A et al (2021). Early predictors of conversion to secondary progressive multiple sclerosis. Mult Scler Relat Disord; 54. DOI: https://doi.org/10.1016/j.msard.2021.103115