Health Technology Briefing
January 2023

Cladribine for treating relapsing-remitting multiple sclerosis

Company/Developer	Merck Serono Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 36094	NICE ID: 11834	UKPS ID: 668705

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Cladribine is in clinical development for the treatment of relapsing-remitting multiple sclerosis (MS). MS is a disease that impacts the brain, spinal cord, and optic nerves, which make up the central nervous system (CNS). The cause of MS is not fully clear, but in MS, the immune system attacks the CNS which causes damage to the nerves. This results in unpredictable symptoms such as numbness, tingling, mood changes, memory problems, pain, fatigue, blindness and/or paralysis. Relapsing remitting MS is where you have relapses (symptoms getting worse) followed by recovery ("remitting"). Relapsing-remitting MS is the most common form of MS.

Cladribine mimics a component of DNA (genetic material). When administered into a patient as an oral tablet, it enters cells and is activated. The active form then accumulates and makes T and B cells (a type of immune cell) susceptible to cell death. In MS, that is thought to interrupt the immune events that are implicated in MS therefore may offer a targeted treatment option.

Proposed Indication

Treatment of relapsing-remitting multiple sclerosis (MS).[1,2]

Technology

Description

Cladribine (Mavenclad) is a nucleoside analogue of deoxyadenosine. A chlorine substitution in the purine ring protects cladribine from degradation by adenosine deaminase, increasing the intracellular residence time of the cladribine prodrug. Subsequent phosphorylation of cladribine to its active triphosphate form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), is particularly efficiently achieved in lymphocytes, due to their constitutively high deoxycytidine kinase (DCK) and relatively low 5'-nucleotidase (5'-NTase) levels. A high DCK to 5'-NTase ratio favours the accumulation of Cd-ATP, making lymphocytes particularly susceptible to cell death. As a result of a lower DCK/5'-NTase ratio other bone marrow derived cells are less affected than lymphocytes. DCK is the rate limiting enzyme for conversion of the cladribine prodrug into its active triphosphate form, leading to selective depletion of dividing and non-dividing T and B cells.[3]

The mechanism by which cladribine exerts its therapeutic effects in MS is not fully elucidated.[3] Cladribine is cytotoxic particularly to lymphocytes and monocytes, inhibiting both DNA synthesis and repair. Its effect on B- and T-lymphocytes is thought to interrupt the cascade of immune events central to multiple sclerosis.[4]

Cladribine was developed for the treatment of relapsing-remitting MS. In the phase III trial CLARITY (NCT00213135), cladribine was administered as a tablet at a cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks, or at a cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at weeks 1, 5, 48, and 52 and placebo matched to cladribine tablet will be administered at week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.[1]

Key Innovation

Treatment benefits and disease modification can be obtained with approved parenteral immunomodulatory and immunosuppressant therapies. However, treatment responses are often less than complete, and concern regarding safety and side-effect profiles may limit the general use of these drugs. The need for parenteral administration may present relative or absolute barriers to access, limiting treatment adherence and long-term outcomes. Results from the phase III trial (NCT00213135) demonstrated that short-course therapy with cladribine tablets provided rapid and sustained treatment benefits for patients with relapsing–remitting MS during a 96-week period.[5] In a network meta-analysis (NMA), cladribine tablets was shown to be more effective than all oral comparators considering the magnetic resonance imaging (MRI) no evidence of disease activity (NEDA) measurement.[6]

Results from the phase III extension trial (NCT00641537) indicate a favourable risk–benefit ratio in relapsing-remitting MS. It also demonstrated that the short-duration dosing of cladribine tablets in Years 1 and 2 resulted in a durable clinical response and provided substantial “treatment-free” periods for at least two additional years with no requirement for a disease-modifying drug; various efficacy analyses indicate that the clinical benefits of cladribine tablets may persist beyond 2 years of observation. The short-

duration posology and favourable risk–benefit profile of cladribine tablets treatment may facilitate treatment adherence, a significant challenge for patients with MS.[7]

If approved, cladribine will provide an alternative treatment option for patients with relapsing-remitting MS.

Regulatory & Development Status

Cladribine is currently licensed as a tablet in the UK for the treatment of adult patients with highly active relapsing MS as defined by clinical or imaging features.[3] It is also licensed as an intravenous (IV) fusion for treatment of adults with hairy cell leukaemia and B-cell chronic lymphocytic leukaemia.[4]

Cladribine is currently in phase II/III clinical trials for the development of:[8]

- other forms of MS
- hairy cell leukaemia
- acute lymphoblastic leukaemia
- acute myeloid leukaemia
- peripheral T-cell lymphoma
- myelodysplastic Syndromes
- langerhans cell histiocytosis of lung
- acute monocytic leukaemia
- lymphomas

Patient Group

Disease Area and Clinical Need

MS is a disease that impacts the brain, spinal cord, and optic nerves, which make up the central nervous system (CNS) and controls everything we do. The exact cause of MS is unknown, but we do know that something triggers the immune system to attack the CNS. The resulting damage to myelin, the protective layer insulating wire-like nerve fibres, disrupts signals to and from the brain. This interruption of communication signals causes unpredictable symptoms such as numbness, tingling, mood changes, memory problems, pain, fatigue, blindness and/or paralysis.[9] Relapsing remitting MS is a type of MS where you have relapses (symptoms getting worse) followed by recovery (that's when it's "remitting"). In relapsing remitting MS people have attacks of new and old symptoms, this is called a relapse. MS doesn't get worse between relapses but after each relapse it can end up worse than before. As time goes on your body finds it harder to repair the damage each relapse brings. Factors that may influence risk of relapse include stress, infection, pregnancy, smoking and low vitamin D.[10]

In 2020, Public Health England (PHE) published statistics that showed MS estimated prevalence is 190 cases per 100,000 population, with 105,800 individuals in England. MS is more than twice as common in females than males, 272 versus 106 per 100,000 population. Females in the 50 to 59 years age group are 3 times more likely than males of a similar age to have MS. 75% of males and females with MS are aged between 40 and 74 years of age. Estimated incidence of MS is between 8 and 11 new cases diagnosed each year in England per 100,000 population. On average 4,950 new cases of MS are diagnosed each year in England.[11] Relapsing remitting MS is the most common type of MS.[10] Around 85% of people with multiple sclerosis are diagnosed with relapsing-remitting MS, therefore using the PHE data, it can be estimated that in 2020, 89,930 people had relapsing-remitting MS.[10,11]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following treatment option for relapsing-remitting MS:[12]

- Diroximel fumarate
- Ponesimod
- Ofatumumab
- Alemtuzumab
- Peginterferon beta-1a
- Cladribine
- Ocrelizumab
- Dimethyl fumarate
- Teriflunomide
- Fingolimod
- Natalizumab

Clinical Trial Information

Trial	**CLARITY EXTENSION STUDY,** NCT00641537; A Phase IIIb, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Extension Trial to Evaluate the Safety and Tolerability of Oral Cladribine in Subjects With Relapsing-Remitting Multiple Sclerosis Who Have Completed Trial 25643 (CLARITY Extension) **Phase III –** Completed **Location(s) –** 23 countries in EU, UK, USA, Canada and other countries. **Study completion date –** December 2011
Trial Design	Randomised, parallel assignment, quadruple-masked
Population	N=867 (actual); 18 Years to 65 Years
Intervention(s)	Cladribine oral tablets
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcomes:** • Safety Population: Percentage of Participants With at Least 1 Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) Grade 4 Hematologic and Hepatic Toxicity [Time Frame: Baseline up to Week 120] • Safety Population: Mean Change From Baseline in Absolute Lymphocyte Count, Platelet, Neutrophils and Leukocytes at Week 120 [Time Frame: Baseline, Week 120] • Safety Population: Mean Change From Baseline in Hemoglobin at Week 120 [Time Frame: Baseline, Week 120] See trial record for full list of outcomes.
Results (efficacy)	Cladribine treatment in CLARITY produced efficacy improvements that were maintained in patients treated with placebo in the extension; in patients treated with cladribine 3.5 mg/kg in CLARITY, approximately 75% remained relapse-free when given placebo during the extension.[7]

Results (safety)	Adverse event rates were generally similar between groups, but lymphopenia Grade ⩾ 3 rates were higher with cladribine than placebo (Grade 4 lymphopenia occurred infrequently). In patients receiving cladribine 3.5 mg/kg in CLARITY and experiencing lymphopenia Grade ⩾ 3 in the Extension, >90% of those treated with cladribine 3.5 mg/kg and all treated with placebo in the Extension, recovered to Grade 0–1 by study end.[7]

Trial	**CLARITY; NCT00213135;** A Phase III, Randomized, Double-blind, Three-arm, Placebo-controlled, Multi-center Study to Evaluate the Safety and Efficacy of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (RRMS) **Phase III –** Completed **Study completion date –** November 2008
Trial Design	Randomised, parallel assignment, triple masked
Population	N = 1326 (actual); Has definite MS according to the 2005 McDonald criteria; Has relapsing-remitting disease with 1 or more relapses within 12 months prior to Study Day 1; 18 Years to 65 Years
Intervention(s)	Cladribine oral tablets
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcomes:** • Annualized Qualifying Relapse Rate [Time Frame: Week 96] See trial record for full list of outcomes.
Results (efficacy)	Among patients who received cladribine tablets (either 3.5 mg or 5.25 mg per kilogram), there was a significantly lower annualized rate of relapse than in the placebo group (0.14 and 0.15, respectively, vs. 0.33; P<0.001 for both comparisons), a higher relapse-free rate (79.7% and 78.9%, respectively, vs. 60.9%; P<0.001 for both comparisons), a lower risk of 3-month sustained progression of disability (hazard ratio for the 3.5-mg group, 0.67; 95% confidence interval [CI], 0.48 to 0.93; P=0.02; and hazard ratio for the 5.25-mg group, 0.69; 95% CI, 0.49 to 0.96; P=0.03), and significant reductions in the brain lesion count on magnetic resonance imaging (MRI) (P<0.001 for all comparisons).[5]
Results (safety)	Adverse events that were more frequent in the cladribine groups included lymphocytopenia (21.6% in the 3.5-mg group and 31.5% in the 5.25-mg group, vs. 1.8%) and herpes zoster (8 patients and 12 patients, respectively, vs. no patients).[5]

Estimated Cost

The NHS indicative price of one cladribine 10mg tablet is £2,047.24.[13]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Diroximel fumarate for treating relapsing–remitting multiple sclerosis (TA794). June 2022.
- NICE technology appraisal. Ponesimod for treating relapsing–remitting multiple sclerosis (TA767). February 2022.
- NICE technology appraisal. Ofatumumab for treating relapsing multiple sclerosis (TA699). May 2021.
- NICE technology appraisal. Alemtuzumab for treating highly active relapsing remitting multiple sclerosis (TA312). May 2014, Last updated: March 2020.
- NICE technology appraisal. Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (TA624). February 2020.
- NICE technology appraisal. Cladribine for treating relapsing–remitting multiple sclerosis (TA616). December 2019.
- NICE technology appraisal. Ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533). July 2018.
- NICE technology appraisal. Beta interferons and glatiramer acetate for treating multiple sclerosis (TA527). June 2018.
- NICE technology appraisal. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320). August 2014.
- NICE technology appraisal. Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303). January 2014, Last updated: June 2014.
- NICE technology appraisal. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (TA254). April 2012.
- NICE technology appraisal. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (TA127). August 2007.
- NICE guideline. Multiple sclerosis in adults: management (NG220). June 2022.
- NICE quality standard. Multiple sclerosis (QS108). January 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies (NHS England Reference: 170079ALG). 2019.

Other Guidance

- Ghezzi A. European and American Guidelines for Multiple Sclerosis Treatment. December 2018.[14]
- American Academy of Neurology. Practice Guideline Recommendations: Disease-Modifying Therapies for Adults With Multiple Sclerosis. April 2018.[15]
- Association of British Neurologists. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. 2015.[16]

Additional Information

References

1 ClinicalTrials.gov. *A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (RRMS) (CLARITY). Trial ID: NCT00213135*. 2005. Available from: https://clinicaltrials.gov/ct2/show/NCT00213135 [Accessed 19th December 2022].

2 ClinicalTrials.gov. *CLARITY Extension Study. Trial ID: NCT00641537*. 2008. Available from: https://clinicaltrials.gov/ct2/show/NCT00641537 [Accessed 19th December 2022].

3 Electronic Medicines Compendium. *MAVENCLAD 10 mg tablets.* 2022. Available from: https://www.medicines.org.uk/emc/product/8435/smpc [Accessed 19th December 2022].

4 British National Formulary. *Cladribine.* 2022. Available from: https://bnf.nice.org.uk/drugs/cladribine/ [Accessed 10th January 2022].

5 Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sørensen PS, et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. *New England Journal of Medicine*. 2010;362(5):416-26. Available from: https://doi.org/10.1056/NEJMoa0902533.

6 Bartosik-Psujek H, Kaczyński Ł, Górecka M, Rolka M, Wójcik R, Zięba P, et al. Cladribine tablets versus other disease-modifying oral drugs in achieving no evidence of disease activity (NEDA) in multiple sclerosis–A systematic review and network meta-analysis. *Multiple Sclerosis and Related Disorders*. 2021;49:102769. Available from: https://doi.org/10.1016/j.msard.2021.102769.

7 Giovannoni G, Soelberg Sorensen P, Cook S, Rammohan K, Rieckmann P, Comi G, et al. Safety and efficacy of cladribine tablets in patients with relapsing–remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. *Multiple Sclerosis Journal*. 2017;24(12):1594-604. Available from: https://doi.org/10.1177/1352458517727603.

8 ClinicalTrials.gov. *Cladribine | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3.* 2022. Available from: https://www.clinicaltrials.gov/ct2/results?term=Cladribine&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 19th December 2022].

9 National Multiple Sclerosis Society. *What is MS?* 2022. Available from: https://www.nationalmssociety.org/What-is-MS [Accessed 19th December 2022].

10 MS Society. *Relapsing remitting MS (RRMS).* 2022. Available from: https://www.mssociety.org.uk/about-ms/types-of-ms/relapsing-remitting-ms [Accessed 19th December 2022].

11 Public Health England. *Multiple sclerosis: prevalence, incidence and smoking status - data briefing.* 2020. Available from: https://www.gov.uk/government/publications/multiple-sclerosis-prevalence-incidence-and-smoking-status/multiple-sclerosis-prevalence-incidence-and-smoking-status-data-briefing [Accessed 19th December 2022].

12 National Institute for Health and Care Excellence. *Multiple sclerosis: Products.* 2022. Available from: https://www.nice.org.uk/guidance/conditions-and-diseases/neurological-conditions/multiple-sclerosis/products?ProductType=Guidance&Status=Published [Accessed 19th December 2022].

13 British National Formulary. *Cladribine: Medicinal forms.* 2022. Available from: https://bnf.nice.org.uk/drugs/cladribine/medicinal-forms/ [Accessed 19th December 2022].

14 Ghezzi A. European and American Guidelines for Multiple Sclerosis Treatment. *Neurol Ther*. 2018 Dec;7(2):189-94. Available from: https://doi.org/10.1007/s40120-018-0112-1.

15 American Academy of Neurology. *Practice Guideline Recommendations: Disease-Modifying Therapies for Adults With Multiple Sclerosis.* 2018. Available from: https://www.aan.com/Guidelines/Home/GuidelineDetail/898 [Accessed 19th December 2022].

16 Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Practical Neurology*. 2015;15(4):273. Available from: https://doi.org/10.1136/practneurol-2015-001139.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.