Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2751

cladribine tablet (Mavenclad®)

Merck

09 May 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

cladribine (Mavenclad®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease as defined by clinical or imaging features.

SMC restriction: for use in patients with active relapsing-remitting multiple sclerosis (RRMS)

In a phase III study, cladribine showed statistically significant improvements in the annualised relapse rate in adults with active relapsing-remitting MS, compared with placebo.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Cladribine is a prodrug and nucleoside analogue, which is activated more efficiently in lymphocytes than in other cell types; this activation leads to the selective depletion of T-cells and B-cells through interference with DNA synthesis, and the consequent induction of apoptosis. This action is thought to interrupt immune system events associated with the progression and relapse of multiple sclerosis (MS).[1, 2]

The recommended cumulative dose of cladribine is 3.5 mg/kg body weight over years 1 and 2 (administered as one treatment course of 1.75 mg/kg per year). Each treatment course includes two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days, where patients take 10 mg or 20 mg orally daily, depending on body weight. After completing the two treatment courses, no further cladribine treatment is required in years 3 and 4; re-initiation of therapy after year 4 has not been studied. See the summary of product characteristics (SPC) for further information..[1]

1.2. Disease background

Multiple sclerosis is a long-term, inflammatory, demyelinating disease of the central nervous system resulting in severe disability due to neurological impairment. MS is the most common cause of serious neurological disability in young adults (usually commencing between 20 and 40 years) and there is currently no cure.[2, 3] Relapsing-remitting MS (RRMS), clinically isolated syndrome and active secondary progressive MS (SPMS), are included in the category of relapsing forms of RMS[4]; RRMS is the by far the most common (approximately 85% of patients) presentation of MS, and is characterised by episodes of symptom flare-ups followed by periods of remission.[2, 5] RRMS can be broken down further into active, highly active and rapidly evolving severe forms.[5, 6, 7] Definitions for disease activity have largely been based on key study inclusion criteria and the number of significant relapses in certain time period (for example active RRMS is defined as ≥2 clinically significant relapses within the past two years); however, international groups have suggested updating the definition of active disease to be based on clinical (relapse) and/or radiological (new or enhancing lesion on MRI) evidence of disease activity.[7] If untreated RRMS often progresses with worsening neurologic disability; it is estimated that over 50% of RRMS patients progress to SPMS within 20 years.[8, 9] RRMS affects women twice as frequently as men.[2, 5]

1.3. Company proposed positioning

The indication under review is an extension (as of 22 March 2024) to the original MHRA licensed indication for cladribine. A submission for the original licensed indication was accepted by Scottish Medicines Consortium (SMC) for restricted use for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features (SMC1300/18). The extended indication now includes patients with active relapsing MS (RMS).[1]

The submitting company has requested that cladribine is restricted for use in patients with active RRMS; this is a subpopulation of the full licensed population.

1.4. Treatment pathway and relevant comparators

The aim of treatment of relapsing forms of MS with disease modifying therapy (DMT) is to reduce the rate and severity of relapses, to delay disease progression, and maintain or improve quality of life. Patients with active RRMS should be offered treatment with DMTs as soon as possible. Higher efficacy DMTs are preferred as first line treatment; these include: ocrelizumab, cladribine, and ofatumumab.[6, 7]

The submitting company considered 12 potential comparators (including best supportive care with no DMT) for this submission. Based on clinical experts consulted by SMC, the most relevant comparators are: dimethyl fumarate (SMC886/13); ofatumumab (SMC2357); ozanimod (SMC2309); ponesimod (SMC2384); teriflunomide (SMC940/14); and ocrelizumab, only if alemtuzumab was contraindicated or otherwise unsuitable (SMC2121).

However, other treatments used in practice include: beta-interferon-1a and -1b (SMC58/03, SMC345/07); diroximel fumarate (SMC2444); glatiramer acetate (SMC1108/15); and peginterferon beta-1a (SMC1018/14).

Ublituximab was accepted for restricted use, for active RRMS, by SMC in January 2025 (SMC2731). Since the company submitted this application for cladribine in October 2024, there is no requirement for them to consider this medicine as a comparator.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of cladribine for this submission comes from the CLARITY study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	CLARITY study.[2, 10]
Study design	International, randomised, double-blind, parallel group, phase III study.
Eligible patients	• Aged 18 to 65 years old. • MRI lesions that are consistent with MS (according to the Fazekas criteria). • Diagnosis of RRMS based on the 2005 McDonald criteria[5] with ≥ 1 relapse in the previous 12 months. • Kurtzke EDSS ranging from 0 to 5.5. • No SPMS or PPMS. • No use of DMTs within three months of entry. • If previously treated, have failed treatments with ≤ 2 DMTs based on efficacy.
Treatments & randomisation	Patients were randomised equally to receive the following oral treatments over 96 weeks: • Cumulative doses of cladribine 5.25 mg/kg bodyweight (unlicensed dose and will not be discussed further) or • Cumulative doses of cladribine 3.5 mg/kg bodyweight or • Matching placebo. Patients in the cladribine cumulative dose of 3.5mg/kg group received 0.875 mg/kg over 4 to 5 days on weeks 1, 5, 48, and 52 of the study; 48 weeks was considered as one year in this study. IV or oral corticosteroids (maximum of 14 days) were permitted to treat acute relapses (based on clinician review). From week 24, patients suffering ≥ 1 relapse and/or a sustained increase in EDSS of ≥ 1, or ≥ 1.5 if baseline EDSS was 0 (over a period of at least three months) could receive rescue treatment with interferon beta-1a; these patients were permanently discontinued from study medication but remained in the study for all the scheduled assessments.

Primary outcome	Annualised rate of relapse (ARR) at 96 weeks. A relapse was defined as an increase in EDSS of two points in at least one functional system or an increase of one point in at least two functional systems (excluding cognition, bowel and bladder function) in the absence of fever, lasting at least 24 hours following 30 days of clinical stability or improvement.
Secondary outcomes	• Proportion of relapse-free patients at week 96. • Time to 3-month confirmed EDSS progression.[a] • Time to 6-month confirmed EDDS progression (post-hoc analysis).[a,b] • Mean number of active T1 gadolinium-enhanced (Gd+) lesions per patient per scan at 96 weeks. • Mean number of active T2 lesions per patient per scan at 96 weeks. • Mean number of combined unique lesions per patient per scan at 96 weeks.
Statistical analysis	Analysis was performed on the ITT population (which included all randomised patients regardless of whether they received treatment) using hierarchical ranking of the primary outcome followed by the secondary outcomes in the order specified above. For patients who received rescue therapy, the primary and secondary efficacy analyses included the pre-rescue data and imputed data from the time of rescue onwards. The responses for patients with missing relapse, EDSS progression, or MRI lesion status were imputed based on data for patients with a known status (that is either free or not free) at the end of 96 weeks.

[a] Defined as the time to sustained change (over a period of at least 3 or 6 months) in EDSS score of ≥ 1 point or ≥ 1.5 points if the baseline EDSS was 0.

[b] This secondary outcome was investigated in a post-hoc analysis which was considered acceptable by the regulator given that the study was conducted prior to the specification of duration in the relevant investigatory guidelines.[11]

DMTs = disease modifying treatments; EDSS = Expanded Disability Status Scale (0 = the lowest score on the scale and indicates normal function; 10 = the highest score and indicates death due to MS); IV = intravenous; ITT = intention to treat; MRI = magnetic resonance imaging; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Detailed results for the licensed cumulative dose of cladribine (3.5 mg/kg bodyweight) and placebo groups are presented in Table 2.2.

Table 2.2. Primary and selected secondary outcomes from the CLARITY study in the ITT population.[2, 10]

	Cladribine – cumulative dose of 3.5 mg/kg bodyweight (n=433)	**Placebo (n=437)**
Primary outcome: annualised rate of relapse (ARR) at week 96.		
ARR (95% CI)	0.14 (0.12 to 0.17)	0.33 (0.29 to 0.38)
Rate ratio (95% CI), p-value	0.43 (0.34 to 0.54), p<0.001	
Secondary outcome: Proportion of relapse-free patients at week 96.		
Proportion without relapse at week 96.	80%	61%
Odds ratio (95% CI), p-value	2.53 (1.87 to 3.43), p<0.001	
Secondary outcome: Time to 3-month confirmed EDSS progression.		
Time to 3-month sustained change in EDSS score; 10th percentile of time to event (KM estimate)	13.6 months	10.8 months
HR (95% CI), p-value	0.67 (0.48 to 0.93), p=0.02	
Secondary outcome: Time to 6-month confirmed EDSS progression (post-hoc analysis).		
Time to 6-month sustained change in EDSS score; 10th percentile of time to event (KM estimate)	Not available	Not available
HR (95% CI), p-value	0.53 (0.36 to 0.79), p<0.0016	

CI = confidence interval; EDSS = Expanded Disability Status Scale (0 = the lowest score on the scale and indicates normal function; 10 = the highest score and indicates death due to MS); HR = hazard ratio; KM = Kaplan-Meier.

The between group differences were statistically significant for all three imaging outcomes, favouring cladribine. Rescue medication use at 96 weeks (an exploratory outcome) was lower in the cladribine group (2.5%, 11/433) compared with the placebo group (6.2%, 27/437).[2, 10]

In a post-hoc analysis, the effect of cladribine on a composite outcome (including no relapses, no 3-month-confirmed EDSS worsening, no new T1 Gd+ lesions and no active T2 lesions) titled No Evidence of Disease Activity (NEDA) was shown to numerically favour cladribine[12]; this outcome was included in the economic analyses.

2.2. Evidence to support the positioning proposed by the submitting company

The submitting company consider the full population from the CLARITY study provides evidence for the licence extension as all patients had active disease. CLARITY included patients with highly active RRMS, a subgroup SMC has previously considered (SMC1300/18).

2.3. Health-related quality of life outcomes

A comparison of cladribine 3.5mg/kg group and placebo group, in terms of multiple sclerosis Quality of Life-54 (a 54-item questionnaire that measures 12 domains: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life and sexual function) scores, showed there was no evidence of a difference, but numbers were small (n=45 [baseline] to n=73 [week 96]). There was a statistically significant difference favouring cladribine in terms of EuroQol-5 Dimensions (EQ-5D) but not in terms of EQ-5D visual analogue scale.[13]

2.4. Supportive studies

CLARITY-EXT was a phase IIIb, international, double-blind, extension study, lasting 2 years (n = 806). The primary objective of this study was safety, while efficacy endpoints were exploratory. Across the 4-year period (CLARITY plus CLARITY-EXT) one small subgroup of patients (n=98) received cladribine 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4, aligning with the licensed dosing. The majority of this small subgroup of patients were relapse-free at the end of year 4. There was no group maintained on placebo throughout CLARITY and CLARITY-EXT for comparison to the licensed regimen.[14]

CLASSIC-MS was an open-label, prospective, follow-up study in patients with active RRMS who were previously enrolled in the CLARITY study with or without participation in CLARITY-EXT. The analysis included 394 patients exposed to cladribine, with a subgroup of 160 patients exposed to 3.5 mg/kg cumulatively, and 41 patients never exposed to cladribine. The primary objective of the study was to assess long-term mobility beyond treatment courses. After a median follow-up of 10.9 years since completing the CLARITY or CLARITY-EXT studies, patients exposed to cladribine were less likely to use further DMTs (56% of the exposed vs. 27% of the non-exposed), with 58% of those receiving cladribine at 3.5 mg/kg for 2 years using no further DMTs.[15]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

Due to the lack of head-to-head studies comparing cladribine with comparator disease modifying therapies (DMTs), the submitting company presented a random-effects network meta-analysis (NMA). The NMA compared cladribine with DMTs accepted for use in NHSScotland for the treatment of active RRMS; these were all deemed to be relevant comparators. A total of 40

studies were included in the NMA, which assessed the following efficacy outcomes: annualised relapse rate (ARR); 3- and 6-month confirmed disability progression; and the safety outcome, all-cause treatment discontinuation. The NMA was used to inform the economic analyses. See table 2.3 for details.

Table 2.3: Summary of indirect treatment comparison.

Criteria	Overview
Design	Random effect network meta-analysis.
Population	Adult patients (≥ 18 years) with a confirmed diagnosis of RRMS (excluded secondary progressive MS without current relapse and clinically isolated syndrome), though active disease is not specified.
Comparators	Interferon beta-1a, interferon beta-1b, glatiramer acetate, peginterferon beta-1a, ofatumumab, ocrelizumab, dimethyl fumarate, diroximel fumarate, teriflunomide, ponesimod, ozanimod.
Studies included	40 studies included.
Outcomes	Annualised relapse rate (ARR); 3-month confirmed disability progression; 6-month confirmed disability progression; all-cause treatment discontinuation.
Results	Overall, the results indicated that cladribine is at least as effective as the other DMTs for all the efficacy outcomes. There was also no clear evidence of a difference in the risk of all-cause treatment discontinuation between cladribine and the other DMTs; except for interferon beta-1a 44 micrograms three times per week which had a higher risk of all-cause treatment discontinuation.

DMTs = disease modifying therapies; MS = multiple sclerosis; RRMS = relapsing remitting multiple sclerosis

3. Summary of Safety Evidence

A final integrated safety analysis has been published that contains safety data combined from the phase III studies: CLARITY; CLARITY-EXT and ORACLE MS [10,14,16, 17]; and the prospective, observational PREMIERE registry (which ran from November 2009 to October 2018, consisting of patients who had participated in at least one of the phase III trials).[18]

The cohort for this analysis consisted of patients with RRMS who received cladribine 3.5 mg/kg (n=923) and placebo (n=641). Overall, the number of patients who reported ≥ 1 serious treatment-emergent adverse event (AE) was higher in the cladribine group (14%) compared with the placebo group (11%). Serious AEs of special interest (presented as cladribine versus placebo) included: lymphopenia (0.4% versus 0.0%), infections and infestations (2.5% versus 1.6%), and malignancies (2.5% versus 0.5%). Serious herpetic infection AEs occurred more frequently in the cladribine group (0.2%) than in the placebo group (0.0%), herpes zoster occurred more frequently during the periods of grade 3 or 4 lymphopenia. The rate of malignancies observed with cladribine in the final integrated safety analysis was not different from the expected rate in the matched GLOBOCAN reference population (standardised incidence ratio of 0.88; 95% CI: 0.44 to 1.69).[18]

Overall, the integrated safety analysis consolidated over 8 years of safety data, identified no new major safety findings, demonstrating the favourable AE profile and long-term safety of cladribine tablets in treatment of RRMS patients. However, there are monitoring requirements as per the SPC. For example, lymphocyte counts need to be monitored before initiating cladribine in year 1 and 2, as well as at 2 and 6 months after the start of treatment in each treatment year.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- The CLARITY study was a double-blind, randomised-controlled, phase III study that appears to have been well-conducted, with stratification and most baseline characteristics were balanced between the two treatment groups; this make it likely that there is a low risk of bias and provides reassurance about the internal validity of the study.
- In the CLARITY study, when compared with placebo, patients with RRMS and active disease who were treated with cladribine had statistically significant and clinically relevant improvements in ARR, and the time to 3-month and 6-month confirmed EDSS progression.[2] The improvements seen in secondary outcomes related to MRI measurements (statistically significant) were also supportive of these positive findings.[2]

4.2. Key uncertainties

- There is no direct evidence comparing cladribine tablets with any relevant comparators for the proposed positioning. The submitting company provided indirect evidence against relevant DMTs and claim that the results support that cladribine is an effective alternative to the other DMTs. The NMA had several limitations related to heterogeneity, sample sizes of some of the studies, uncertainty around long-term efficacy and safety and wide confidence intervals. However, despite these limitations, the company's conclusion, that cladribine is an effective alternative, appears reasonable.
- The longer-term effects of cladribine are uncertain. There is no robust controlled data beyond 96 weeks. The extension study and longer-term study provide some evidence, but they have important limitations, including relating to risk of bias, low patient numbers with the licensed dosing regimen and the data need to be interpreted with caution. Re-initiation of cladribine after year 4 has not been studied.
- There is some uncertainty around the generalisability of the CLARITY study results to the proposed Scottish population. The CLARITY study included patients with highly active disease, this subpopulation was reviewed by SMC in 2018 and are not a part of the proposed population. Results for the highly active group are included in the ITT population and may not reflect relative efficacy outcomes in the population with less active disease.

4.3. Clinical expert input

The majority of clinical experts consulted by SMC considered that cladribine tablets are not a therapeutic advancement based on the availability of other effective DMTs for active RRMS, and that cladribine is already used for highly active RRMS. Clinical experts indicated cladribine would be a useful option for patients who are: needle phobic, intolerant of other oral medicines (for example dimethyl fumarate), planning pregnancy more than 6 months after the cladribine course, busy lifestyle frequent travellers, or live in geographically remote locations.

4.4. Service implications

Clinical experts consulted by SMC highlighted the limited burden of the oral cladribine dosing regimen compared to other regimens which are more resource intense in terms of administration.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from the Multiple Sclerosis Trust (MS Trust) and the MS Society, both organisations are registered charities.
- The MS Trust has received 24% pharmaceutical company funding in the past two years, including from the submitting company. The MS Society has received 0.01% pharmaceutical company funding in the past two years, including from the submitting company.
- Multiple sclerosis (MS) is a fluctuating, life-long progressive neurological condition. Any MS relapse has the potential to be devastating and profoundly disabling, although the severity and frequency of relapses are largely unpredictable. It has an impact on a person's daily activities, their social life and their ability to remain in employment.
- There are no treatments that can cure MS. Treatment goals are to reduce the risk of a relapse to a minimum. There are a range of DMTs available. Patient groups support the expansion of patient choice so that if one treatment option for relapsing MS is contraindicated or not tolerated, then patients and neurologists have other options.
- The administration method of cladribine offers advantages to people with MS as it only involves two treatment courses of oral tablets over two years. Each treatment course consists of two treatment weeks which are one month apart at the beginning of each treatment year. This approach has a minimal impact on everyday life.
- All DMTs carry different levels of risk and efficacy, decisions on which DMT to take are determined by a variety of factors and the availability of cladribine adds to this choice.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 below describes the economic analysis.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	50 years
Population	Cladribine tablets are positioned for active RRMS population.
Comparators	There are 12 DMT comparators included in this submission, as well as best supportive care (BSC). The DMTs were: dimethyl fumarate, glatiramer acetate, interferon beta (including Rebif®, Avonex®, Betaseron®, Extavia®, and peginterferon beta-1a), teriflunomide, ocrelizumab, ofatumumab, ponesimod, diroximel fumarate, and ozanimod. SMC clinical experts indicated the most relevant comparators in Scottish clinical practice are ocrelizumab, ofatumumab, ozanimod, ponesimod and dimethyl fumarate.
Model description	The economic model evaluates cost-effectiveness using a Markov-based cohort approach with 11 health states; 10 disability levels based on the EDSS tool and a death state. The model consists of a natural history model, representing BSC where patients can progress, maintain, improve on their EDSS health states or die based on the diseases natural course. This was based on a study by Palace et al.[20] No subsequent treatments were modelled.
Clinical data	Clinical evidence for cladribine was primarily sourced from CLARITY, which compared cladribine to placebo (a proxy for BSC). Parameters directly sourced from CLARITY include relapse duration, odd ratios for rescue therapy, cladribines discontinuation rate and adverse event rate.

	As there was no direct evidence comparing cladribine to other DMTs, an NMA was conducted to estimate the effectiveness and discontinuation rate for cladribine and comparators against placebo. Data from CLARITY and the comparators' key clinical studies were used to generate the hazard ratio for 6-month CDP and relative risk ratios for ARR. Adverse event rates for each comparator were derived from the NMA's list of sources.
Extrapolation	Hazard ratios generated from the NMA were applied to the natural history model to create the treatment-adjusted model for each comparator and cladribine. Each hazard ratio adjusted the rate of disease progression and relapse in the natural history model based on the comparative effectiveness of each treatment against placebo. This allows the treatment-adjusted model to reflect the differing impact of each treatment. Treatment effects waned over time, with a 25% reduction between years 4-5 and 50% after year 5, altering outcomes in the treatment-adjusted model only. Patients in the treatment-adjusted model transition to the BSC natural history model if they discontinue treatment or reach EDSS state 7+. Long-term discontinuation rates for the comparators were also taken from the NMA, where it is assumed the discontinuation rate is constant across the lifetime horizon for each comparator. However, Cladribine discontinuation rate was sourced from CLARITY and only applied to year 1 in the model. Mortality was modelled to increase with age, using general population mortality adjusted for MS-related excess mortality, and did not vary by EDSS state.
Quality of life	EQ-5D-3L data was taken from the CLARITY study for EDSS health states 0-5. These utility values are the same across both the treatment-adjusted model and natural history model. For EDSS health states 6-8, Hawton et al (2016)[21] was used as a source of utility values, and for EDSS state 9 Orme et al[22] was used. Orme et al was also used to inform the utility for relapses. AE disutilities were sourced from a literature search of pervious appraisals.
Costs and resource use	Costs included medicine acquisition, administration, monitoring, adverse events, resource use and health state unit costs for cladribine and all comparators.
PAS	No patient access scheme (PAS) was proposed by the submitting company. PAS discounts are in place for teriflunomide, ponesimod, ozanimod, diroximel fumarate, dimethyl fumarate, ofatumumab, ocrelizumab and these were included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

Table 6.2 presents the base case economic results and table 6.3 the sensitivity analysis. SMC considered results for decision-making that took into account all relevant PAS. Where the comparator is not subject to a confidential PAS discount, the incremental cost-effectiveness ratio (ICER) is shown. Where the comparator is subject to a confidential PAS discount, SMC is unable to present these results due to competition law issues.

The main QALYs drivers come from improvements in EDSS states 0, 1, 2 for cladribine compared to comparators. The main cost drivers come from medicine acquisition costs as well as differences in direct medical cost for each comparator.

Table 6.2: Base case results

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
cladribine tablets	103,490	10.258	-	-	-
BSC	59,257	9.269	44,233	0.990	44,689
interferon beta-1a 22 µg	90,176	9.566	13,314	0.692	19,236
peginterferon	90,018	9.894	13,472	0.365	36,955
glatiramer acetate	90,481	9.650	13,009	0.474	21,396

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
interferon beta-1a 30 µg	90,502	9.666	12,988	0.592	21,938
interferon beta-1a 44 µg	93,648	9.532	9,842	0.726	13,547
interferon beta-1b 250 µg	99,847	10.112	3,643	0.146	24,954
teriflunomide	CiC	9.500	CiC	0.759	CiC
ponesimod	CiC	9.688	CiC	0.570	CiC
ozanimod	CiC	9.357	CiC	0.901	CiC
diroximel fumarate	CiC	9.769	CiC	0.490	CiC
dimethyl fumarate	CiC	9.784	CiC	0.474	CiC
ofatumumab	CiC	9.997	CiC	0.261	CiC
ocrelizumab	CiC	10.095	CiC	0.163	CiC

Abbreviations - BSC = best supportive care; ICER = incremental cost-effectiveness ratio; RRMS = relapsing-remitting multiple sclerosis; QALYs = quality-adjusted life years; µg = micrograms; CiC = commercial in confidence

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Table 6.3 below.

Table 6.3 Scenario analyses against selected comparators

	Parameter	Base case	Scenario
1	Model structure	11-state model structure	21-state with British Columbia data for RRMS
2	NMA model type	Random effect model	Fixed effect models
3	NMA estimates	HRs and RR use mean estimates from NMA (6-month CPD and ARR)	Upper confidence interval from NMA (6-month CDP and ARR) applied to all treatments
4	Mortality	Mortality is fixed	Mortality by EDSS state
5	Discontinuation	Discontinuation rate estimated using CLASSIC-MS data (5.61%)	Discontinuation rate for cladribine extended to full time horizon (4.85%)
6			No long-term discontinuation rate for cladribine (original base case)
7	Treatment waning	No waning between 0-4 years, 4-5 years 25% waning, 5 years + 50% waning	No waning between Years 0-4, 50% waning Year 4-5, 75% waning Year 5-10, and 90% waning 10+
8			Waning: 100% treatment effect Years 0-4, 50% waning Year 4-5, and 75% waning Year 5+
9	Utility sources	Utility CLARITY (EDSS states 0-5) Hawton et al (6-8), Orme et al (state 9)	Utility (Orme 2007 only)
10	Caregiver disutility	Care giver disutility excluded	Caregiver disutility included
11	Time horizon	50-year lifetime horizon	10-year time horizon
12	NMA estimates	NMA unadjusted for baseline characteristics	Baseline risk-adjusted NMA estimated used
12	Subsequent treatments	No subsequent treatments modelled	Treatment sequencing “basket” included

Abbreviations - Incr.= incremental; CDP = confirmed disability progression; ARR = annualised relapse rate; EDSS = expanded disability status scale; NMA = network meta-analysis.

6.4. Key strengths

- The comparators included in the analysis were appropriate and aligned with the clinical experts' opinions regarding the treatments used in the target population for the proposed positioning.
- The use of a Markov model was a suitable approach for capturing disease progression.
- The simplification of the model to the 11-states structure, by combining RRMS and SPMS progression, was appropriate given the positioning of the submission.
- The company's approach to health state utility values was appropriate, using EQ-5D data from CLARITY for health states 0 to 5, and supplementing the other health states with relevant sources.

6.5. Key uncertainties

- There was no direct head-to-head study data comparing cladribine to any of the relevant comparators. Instead, an NMA was conducted to evaluate comparative efficacy and safety. This introduced inherent uncertainty due to heterogeneity between the studies and producing wide confidence intervals for some of the outcomes. Scenario analysis using the upper confidence intervals from the NMA (scenario 3) showed a notable reduction in the incremental quality-adjusted life-years (QALYs) for cladribine compared with the comparators. This highlights the sensitivity of the results to the choice of NMA estimate and the potential impact on the cost-effectiveness.

- The economic model for cladribine was viewed as lacking face validity, as there was a disconnect between the NMA results and the cost-effectiveness estimates. While the NMA ranks cladribine mid-range among 13 comparators, the economic model suggests it has greater QALY benefits than all treatments, including those ranked higher in efficacy. This discrepancy arose from key modelling assumptions around treatment discontinuation, treatment waning, and the absence of modelled subsequent treatments. While the company provided some justification for these assumptions on an individual basis, their combined impact meant that it was unclear if the modelled treatment pathway aligned with expected clinical reality. Scenario 11 shortened the time horizon to 10 years to try and gauge the impact of removing the compounding impact of the assumptions over time. That changed the results significantly, indicating that these uncertain long-term assumptions were a key driver in the model.

- Collectively, these assumptions related to treatment discontinuation, treatment waning, and the absence of modelled subsequent treatments limited the robustness of the cost-effectiveness evaluation, making it difficult to determine the true comparative value of cladribine.

7. Conclusion

After considering all the available evidence, the Committee accepted cladribine for restricted use in NHSScotland.

8. Guidelines and Protocols

In 2022, NHS Greater Glasgow & Clyde published guidelines: Disease Modifying Treatments (DMTs) in Relapsing-Remitting Multiple Sclerosis (RRMS).[6]

In 2024, the Association of British Neurologists (ABN) published updated guidance - Using disease-modifying treatments in multiple sclerosis: Association of British Neurologists (ABN).[7]

9. Additional Information

9.1. Product availability date

22 March 2024.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Cladribine 10 mg tablets	**3.5 mg/kg bodyweight orally over years 1 and 2.** **Administered as one treatment course of 1.75 mg/kg per year. Each treatment course is two treatment weeks in the first two months of each year.**	**Course 1 (year 1): 28,661** **Course 2 (year 2): 28,661**

Costs from BNF online on 02 February 2025. Costs are based on a bodyweight of 70 kg.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 8,412 patients eligible for treatment with cladribine in year 1 and 8,487 patients in year 5. SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 March 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates

separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.