

cladribine 10mg tablet (Mavenclad®)

SMC No 1300/18

Merck

12 January 2018

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

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

Indication under review: treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

SMC restriction:

- Patients with rapidly evolving severe relapsing-remitting MS: patients with two or more relapses in the prior year whether on treatment or not, and at least one T1 gadolinium-enhancing lesion.
- Patients with sub-optimal therapy relapsing-remitting MS: patients with one or more relapses in the previous year while on disease modifying therapy, and at least one T1 gadolinium-enhancing lesion or nine T2 lesions.

In a phase III study cladribine showed superiority over placebo in terms of annualised relapse rate in patients with high disease activity relapsing-remitting multiple sclerosis.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.¹

Dosing Information

Treatment with cladribine must be initiated and supervised by a physician experienced in the treatment of MS.

The recommended cumulative dose of cladribine is 3.5mg/kg body weight over two years, administered as one treatment course of 1.75mg/kg per year. Each treatment course consists of 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 four or five days on which a patient receives 10mg or 20mg (one or two tablets) as a single daily dose, depending on body weight.

Following completion of the two treatment courses, no further cladribine treatment is required in years three and four. Re-initiation of therapy after year four has not been studied. Initiating and continuing therapy is dependent on appropriate lymphocyte counts.¹

Treatment with cladribine must be initiated and supervised by a clinician experienced in the treatment of MS. For further information please see Summary of Product Characteristics.¹

Product availability date

September 2017

Summary of evidence on comparative efficacy

Cladribine is a pro-drug and purine analogue, which is activated more efficiently in lymphocytes than in other cells types, leading to selective depletion of T- and B-cells through interference with DNA synthesis and consequent induction of apoptosis. This action is thought to interrupt immune system actions associated with progression and relapse of MS.¹

MS is a complex, unpredictable, chronic, immune mediated, demyelinating disease of the central nervous system causing disability and neurological impairment. Relapses can last days to weeks, occur intermittently over many years, and symptoms include weakness, sensory loss, visual loss, and imbalance. Functional disability can accumulate and lead to the onset of secondary progressive multiple sclerosis.²

The submitting company has requested that SMC considers cladribine when positioned for use in two specified subgroups within the group of patients with high disease activity relapsing remitting MS (HDA-RRMS). These two relevant subgroups do not account for all patients in the HDA-RRMS group and are described as follows:

- rapidly evolving severe-RRMS (RES-RRMS), defined as two or more relapses in the prior year whether on treatment or not, and at least one T1 gadolinium-enhancing (Gd+) lesion.
- sub-optimal therapy-RRMS (SOT-RRMS), defined as one or more relapses in the prior year while on disease modifying therapy (DMT), and at least one T1Gd+ lesion or nine T2 lesions.

The pivotal study, CLARITY, was of multicentre, double-blind, phase III design, where patients were randomised equally to receive cladribine cumulative oral doses of either 3.5mg/kg or 5.25mg/kg (unlicensed dose and not discussed further) of body weight or placebo over 96 weeks. Patients were aged 18 to 65 years, had a diagnosis of MS based on the Fazekas criteria, had at least one relapse in the previous 12 months but relapse free in the month preceding the study, had not taken a DMT within three months of commencing the study, and had an expanded disability status score (EDSS) ranging from 0 to 5.5 (with zero being the lowest score on the scale, indicating normal function and ten being the highest, indicating death due to MS). Patients in the cladribine cumulative dose of 3.5mg/kg group received 0.875mg/kg over 4 to 5 days on weeks 1, 5, 48 and 52. ^{3 4 5}

The primary outcome was the 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. Results of the primary outcome are shown in table 1, and important secondary outcomes in the relevant subgroup are shown in table 2 below. The HDA-RRMS group included patients with two or more relapses in the previous year regardless of treatment status, or patients with one or more relapses in the previous year while on DMT and ≥ 1 T1 Gd+ or ≥ 9 T2 lesions.

The RES-RRMS and SOT-RRMS groups are subgroups of the HDA-RRMS group, which is a subgroup of the intention-to-treat/overall population. SMC is unable to present the results of the primary outcome or the secondary outcomes from the post hoc analysis in the RES-RRMS and SOT-RRMS subgroups as these are considered as commercial in confidence.

Table 1. Annualised rate of relapse at 96 weeks, the primary outcome from the CLARITY study in the overall population and in relevant subgroup. ^{3 4 6}

Population	Cladribine 3.5mg/kg (licensed dose)	Placebo	Rate ratio (95% CI), p-value
Intention-to-treat population, ARR	(n=433) 0.14	(n=437) 0.33	0.43 (95% CI: 0.34 to 0.54), p<0.001
HDA-RRMS subgroup, ARR	(n=140) 0.16	(n=149) 0.47	0.33 (95% CI: 0.23 to 0.48) p<0.0001

ARR=annualised rate of relapse, CI=confidence interval, HDA=high disease activity, RRMS=relapsing-remitting multiple sclerosis

Table 2. Important secondary outcomes from ITT analysis and post-hoc analysis in HDA subgroup

Secondary outcome	ITT analysis ^{3 4}		HDA-RRMS subgroup ^{4 6}	
	Cladribine 3.5mg/kg	Placebo	Cladribine 3.5mg/kg	Placebo
Relapse-free patients at 96 weeks, % (n/N)	80% (345/433)	61% (266/437)	<u>CIC*</u>	<u>CIC*</u>
	Odds ratio 2.53 (95% CI: 1.87 to 3.43) p<0.001		NR	
Time to three-month sustained change in EDSS score; 10 th percentile of time to event (K-M), months	13.6	10.8	NR	NR
	Hazard ratio 0.67 (95% CI: 0.48 to 0.93) p=0.02		Hazard ratio 0.28 (95% CI: 0.15 to 0.54) p=0.0001	
Time to six-month sustained change in EDSS score; (K-M estimates) (post hoc)	Hazard ratio 0.53 (95% CI: 0.36 to 0.79), p=0.0016		Hazard ratio 0.18 (95% CI: 0.07 to 0.43) p=0.0001	
Rescue medication use, % (n/N)	2.5% (11/433)	6.2% (27/437)	<u>CIC*</u>	<u>CIC*</u>

ITT=intention-to-treat, HDA=high disease activity, EDSS=expanded disability status scale, K-M=Kaplan-Meier, CI= confidence interval, CIC=commercial in confidence results NR=not reported

MRI measurements are not a validated surrogate outcome of clinical value but are a useful tool to evaluate consistency with clinical effect.⁷ In the ITT analysis patients who received cladribine 3.5mg/kg cumulative dose had statistically significantly fewer lesions compared with the placebo group in the following MRI measurements; T1 Gd+ lesions, T2-weighted lesions and combined unique lesions.^{3 4}

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 statistically significant difference, but numbers were small (n=45 to 73 from baseline to 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.⁸

CLARITY-EXT was a phase IIIb extension study, lasting two years, randomising patients that had participated in CLARITY to various treatments arms. The aim of this study was to further evaluate the safety and tolerability of oral cladribine, as well as to evaluate the prolonged clinical benefit in patients receiving an additional 96 weeks of treatment following the 96 weeks of treatment in CLARITY. A small subgroup of patients (n=98) match the licensed regimen and received two courses of cladribine in CLARITY and placebo in CLARITY-EXT. For this subgroup the ARR was 0.15 at week 96 of CLARITY-EXT and 76% (68/98) of patients were relapse free during CLARITY-EXT. The median gap between the studies was 39.7 weeks (0.3 to 118) and patients could have received another DMT in the gap period as long as there was a three month washout period.⁹ There was no group maintained on placebo throughout CLARITY and CLARITY-EXT for comparison to the licensed regimen. The numbers of patients in the RES-RRMS and SOT-RRMS subgroups in CLARITY-EXT (who received the licensed dose of cladribine) were small.¹⁰

In a post hoc analysis the effect of cladribine on a free from disease activity endpoint (a composite endpoint including absence of relapse, no three-month sustained change in EDSS score and no new MRI lesions) was shown to be significant across all patient subgroups. The patient subgroups included

those with individual or a combination of disease characteristics indicative of high disease activity such as; previous treatment status, baseline EDSS and baseline T1Gd+ lesions.¹¹

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

In the cladribine 3.5mg/kg and placebo groups any adverse event occurred in 81% (347/430) versus 73% (319/435) of patients and serious treatment-emergent adverse events occurred in 8.4% (36/430) versus 6.4% (28/435), respectively. Adverse events that led to treatment discontinuation occurred in 3.5% versus 2.1% of patients in the cladribine 3.5mg/kg and placebo groups, respectively.

The following adverse events occurred in the cladribine 3.5mg/kg and placebo groups respectively; headache 24% (104/430) versus 17% (75/435), lymphocytopenia 22% (93/430) versus 1.8% (8/435), nasopharyngitis 14% (62/430) versus 13% (56/435), serious infections and infestations 2.3% (10/430) versus 1.6% (7/435), and neoplasms (benign, malignant or unspecified) 1.4% (6/430) versus 0% (0/435). Of the six neoplasms in the cladribine 3.5mg/kg group there was one case each of melanoma, carcinoma of pancreas and carcinoma of ovary, whilst on study treatment.

For patients on the licensed regimen of cumulative 3.5mg/kg of cladribine, from the CLARITY-EXT study 16% (16/98) reported severe adverse reactions.¹²

Summary of clinical effectiveness issues

A number of DMTs are licensed and have been accepted for use by SMC for the treatment of MS. Their licensed indications vary and some are more specific. Treatments include interferon beta-1a, interferon beta-1b, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, natalizumab, daclizumab and alemtuzumab, which all, to varying extents, reduce relapse rate and MRI lesion accumulation in patients with RRMS.

Patients with active disease (≥ 2 relapses in previous two years) should be considered for treatment with DMT. These may be divided into those with moderate efficacy (beta interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod) and high efficacy (alemtuzumab and natalizumab). Patients are generally commenced on a moderate efficacy medicine with choice depending on patient and disease factors. Those with more active RRMS may be considered for a high efficacy medicine. The risk/benefit profile should be considered by patients and clinicians before choosing a DMT.²

The submitting company has requested that SMC considers cladribine when positioned for use in the RES-RRMS and SOT-RRMS subgroups of HDA-RRMS.

In CLARITY the licensed dose of cladribine showed a statistically significant reduction in ARR compared with placebo in the ITT analysis and the HDA-RRMS subgroup. Cladribine also showed favourable, statistically significant results in time to three-month sustained change in EDSS score in the ITT analysis and HDA-RRMS subgroup.

In a post hoc analysis the effect of cladribine on a free from disease activity endpoint was shown to be significant across all patient subgroups, stratified by baseline demographics and disease characteristics.¹¹

The CLARITY study has some limitations. Bowel and bladder impairment were omitted from EDSS scoring when measuring the primary outcome.⁷ There were differences in some baseline characteristics of patients in the cladribine 3.5mg/kg and placebo groups, such as EDSS scores, time since first attack and previous DMT.

Patient numbers in the RES-RRMS and SOT-RRMS subgroups, which were used for decision making, were small and the analyses were post hoc. SMC is unable to present the results in these groups as they are considered as commercial in confidence. Follow-up of patients was not sufficiently long to gauge the long term impact of cladribine on disease progression. In CLARITY, a small proportion of patients had received prior treatment with DMTs, which included interferon beta or glatiramer acetate.³ The European Medicines Agency noted that sequential use of various DMTs may substantially increase the risk for development of malignancies and opportunistic infections such as progressive multifocal leukoencephalopathy. Consequently, sequential use of cladribine and other immunosuppressive or immunomodulatory agents is to be studied in a long-term post authorisation safety study.⁴

Limitations of the CLARITY-EXT study include; confounding and bias in recruitment by the loss of patients who did not tolerate or respond to cladribine, the lack of a placebo group for comparison, the gap period between studies, patients may have taken another DMT in this gap period but required a 3 month washout period prior to entering CLARITY-EXT and the numbers in the relevant subgroups were small. Results from CLARITY-EXT should therefore be interpreted with caution.⁶

A post-authorisation safety study is to be conducted to provide data for cladribine versus fingolimod which may provide clarity in terms of the malignancy risk of cladribine.⁴

There are no direct comparative data for cladribine versus active comparators. The submitting company presented Bayesian network meta-analyses (NMA) to compare the efficacy of cladribine to alemtuzumab, natalizumab, daclizumab, and fingolimod for RES-RRMS and to fingolimod for SOT-RRMS. Results from the NMA for the primary outcome of ARR were used in the economic model. The number of studies included in the NMA was 10 for the RES-RRMS network and three for the SOT-RRMS network. The fixed effects model was preferred for these subpopulations. Results for ARR indicate no evidence that cladribine is superior to any comparator in the RES-RRMS and SOT-RRMS sub populations (as credible intervals included one for all comparisons of cladribine versus active comparator). Limitations of the NMA include heterogeneity between studies in terms of a number of baseline characteristics and outcomes in some common control arms and a wide variation in the years when the studies were conducted. Another limitation was the reporting of results of the NMA in the company's submission which was inconsistent. Finally for the SOT-RRMS subpopulation only a comparison of cladribine versus fingolimod was possible and assumptions were made, for the economic model, for the comparison versus daclizumab and alemtuzumab.

For six month confirmed disability progression endpoint a meta-regression analysis was undertaken due to limited subgroup data reported for comparator studies. Results indicate no evidence that cladribine is superior to any comparator in the RES-RRMS and SOT-RRMS sub-populations for this endpoint.

Cladribine is a cytotoxic medicine. Pregnancy prevention is required for males and females, as it has been shown to be embryo-lethal in pregnant mice and teratogenic in mice and rabbits, and there are safe handling requirements. Cladribine is administered orally and the regimen of four short treatment periods (of four or five days) over two years may be an advantage to patients compared to other treatments that are given more frequently and/or by parenteral administration. Lymphocyte counts need to be monitored before initiating cladribine in year one and two, as well as at two and six months after the start of treatment in each treatment year.¹

Clinical experts consulted by SMC considered that cladribine is an advancement due to its oral administration regimen and its favourable side-effect and withdrawal profile. Experts considered that cladribine would reduce pressure on services associated with administration of parenteral alternatives and would support compliance to treatment. They considered cladribine would be used as an alternative to fingolimod, alemtuzumab, natalizumab and daclizumab.

Other data were also assessed but remain commercially confidential.*

Summary of comparative health economic evidence

The company submitted a cost-utility analysis (CUA) comparing cladribine to natalizumab, alemtuzumab, fingolimod and daclizumab for the treatment of adult patients with RES-RRMS and comparing cladribine to fingolimod, daclizumab and alemtuzumab for the treatment of adult patients with SOT-RRMS. The analysis was based on a Markov state transition model which contained 11 health states representing patients' EDSS status. In each yearly cycle, patients could transition from one EDSS state to another (i.e. experience improvement or deterioration of their disease status), remain in their current EDSS state, or die. Patients were also assigned a probability of experiencing acute relapses which were modelled independently of EDSS disability progression. The model assumed treatment discontinuation due to disease progression when patients reached EDSS 7 or due to other reasons. After stopping the treatment, patients went on to receive best supportive care (BSC) and were assigned progression and relapse rates of natural disease course. The time horizon was 50 years.

The clinical data used in the model were derived from a number of sources. Annualised relapse rates for BSC were from the CLARITY study and these were adjusted for treatment effect based on results from the NMA. Natural disease progression (i.e. transition probabilities for EDSS health states) were from the British Columbia Multiple Sclerosis registry and were adjusted for treatment effect based on a meta-regression that included studies of individual comparators that reported six-month confirmed disease progression. The model also included waning of medicine efficacy that was informed by published literature.

Within the base case analysis utility values for EDSS 0 to EDSS 5 were taken from the pivotal study and extension study, however due to the lack of available utility values for EDSS 6 to 9, these were taken from published literature. Within the CLARITY studies, the EQ-5D-3L was used to collect quality of life data from patients at study day 1, weeks 24, 48, 72, 96 (termination visit) and at each relapse evaluation. Disutilities associated with adverse events were included in the company's base case analysis.

The analysis included medicine acquisition costs that were estimated based on patient weight distribution within the CLARITY study. Direct medical costs and non-medical costs were included. These were dependent on the time patients spent in each of the EDSS health states and with relapse events. Adverse event costs associated with all treatments were included in the analysis.

Patient access scheme (PAS) discounts are in place for fingolimod and daclizumab and these were included in the results used for decision-making by SMC by using estimates of the comparator PAS discounts.

The base case results in the RES-RRMS and SOT-RRMS subgroups indicated that cladribine dominated the comparators (i.e. cladribine was more efficacious and less costly). The results of pairwise comparisons are shown in tables 3 and 4. It should be noted that the company's base case results included carer disutilities and non-medical costs that would not normally be considered as part

of SMC's preferred base case. As such, these assumptions were excluded from the results, but the impact of inclusion of carer disutilities and non-medical costs is shown in tables 5 and 6.

Table 3. Results compared to cladribine at list prices – RES-RRMS

Technology	Incremental costs versus cladribine	Incremental quality adjusted life years (QALYs) versus cladribine	ICER versus cladribine
Alemtuzumab	-£11,541	0.16	Cladribine dominates
Daclizumab	-£48,338	0.84	Cladribine dominates
Fingolimod	-£36,896	1.20	Cladribine dominates
Natalizumab	-£106,545	0.47	Cladribine dominates

ICER=incremental cost-effectiveness ratio, QALY=quality adjusted life year. A positive sign in the incremental costs/QALYs column indicates that cladribine is more costly or more efficacious than the comparator medicine.

Table 4. Results compared to cladribine at list prices – SOT-RRMS

Technology	Incremental costs versus cladribine	Incremental QALYs versus cladribine	ICER versus cladribine
Alemtuzumab	-£11,337	0.14	Cladribine dominates
Daclizumab	-£41,365	0.50	Cladribine dominates
Fingolimod	-£29,767	0.86	Cladribine dominates

ICER=incremental cost-effectiveness ratio, QALY=quality adjusted life year. A positive sign in the incremental costs/QALYs column indicates that cladribine is more costly or more efficacious than the comparator medicine.

The company performed one-way, two-way, scenario and probabilistic sensitivity analyses. In almost all scenarios, cladribine was a dominant treatment option. The analyses appeared to be most sensitive to varying the effect on disease progression that have alemtuzumab, natalizumab and cladribine, discounting, progression adjustment for subgroups and baseline risk.

Table 5. Scenario analysis results including carer disutilities and direct non-medical costs – RES-RRMS, at list prices

Technology	Incremental costs versus cladribine	Incremental QALYs versus cladribine	ICER versus cladribine
Alemtuzumab	-£19,008	0.179	Cladribine dominates
Daclizumab	-£87,808	0.903	Cladribine dominates
Fingolimod	-£92,847	1.288	Cladribine dominates
Natalizumab	-£129,109	0.498	Cladribine dominates

ICER=incremental cost-effectiveness ratio, QALY=quality adjusted life year. A positive sign in the incremental costs/QALYs column indicates that cladribine is more costly or more efficacious than the comparator medicine.

Table 6. Scenario analysis results including carer disutilities and direct non-medical costs – SOT-RRMS, at list prices

Technology	Incremental costs versus cladribine	Incremental QALYs versus cladribine	ICER versus cladribine
Alemtuzumab	-£17,420	0.150	Cladribine dominates
Daclizumab	-£65,256	0.532	Cladribine dominates
Fingolimod	-£70,761	0.922	Cladribine dominates

ICER=incremental cost-effectiveness ratio, QALY=quality adjusted life year. A positive sign in the incremental costs/QALYs column indicates that cladribine is more costly or more efficacious than the comparator medicine.

The results presented above do not take account of the PAS for fingolimod and daclizumab as SMC is unable to present the results provided by the company which used estimates of the comparator PAS prices due to commercial confidentiality and competition law issues.

The main weaknesses include:

- Given the lack of direct clinical trial evidence against the comparator treatments, the CUA was based on the findings of an NMA and a meta-regression analysis and, as noted above, these were associated with some weaknesses. It should also be noted that there was no direct or indirect evidence that would confirm cladribine being superior to any of the comparators. The numerical differences in the ARR and mainly in the disability progression were used to generate QALY differences in the analyses although there was a substantial overlap in the credible intervals. After taking account of these issues, a cost-minimisation approach may have been more appropriate to assess the cost-effectiveness of cladribine. The submitting company subsequently provided scenario analyses assuming no differences in treatment effects on ARR and confirmed disability progression between cladribine and comparators, and between cladribine, comparators and placebo which also showed cladribine being cost- saving (at list prices).
- While the cost-minimisation analysis was principally used to inform SMC decision-making, a number of issues were noted with the cost-utility analysis the company provided, as noted below:
 - The company’s base case cost-utility analysis included carer utilities and non-medical costs which captured informal care (productivity losses), costs of investments on home modifications and medical devices, and costs of professional care. It was noted that exclusion of carer utilities or non-medical costs have non-negligible impact on the results and excluding them may represent a more relevant base case for decision-making. The figures excluding carer disutilities and non-medical costs are presented in tables 3 and 4.
 - Many of the sensitivity analyses were carried out around the company’s base case and it is therefore difficult to assess the potential impact of individual scenarios and variables if these were varied around the base case relevant for decision-making.
 - The use of different proportions of patients re-initiating treatment with cladribine and alemtuzumab after year 2 was based on limited evidence. Using the same proportion of patients for cladribine and alemtuzumab had only little impact on the results. This scenario is, however, a more conservative assumption as excluding re-initiation of cladribine would result in its lower costs.

Despite the weaknesses outlined above, taking account of additional scenario analyses and clarification provided by the submitting company, the economic case has been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and carer involvement

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

- We received a patient group submission from the Multiple Sclerosis Trust (MS Trust) and a joint patient group submission from the MS Society and Revive MS Support. All three organisations are registered charities.
- The MS Trust has received 5.8% pharmaceutical company funding in the past two years, including from the submitting company. Revive MS Support has received 3.4% pharmaceutical company funding in the past two years with none from the submitting company. The MS Society has received less than 0.5% pharmaceutical company funding in the past two years, including from the submitting company.
- Multiple sclerosis (MS) is a fluctuating, life-long progressive neurological condition. People with MS may experience issues with mobility, balance, pain, fatigue and visual and cognitive impairment. It is a complex unpredictable condition which has an impact on a person's daily activities, their social life and their ability to remain in employment, resulting in considerable psychosocial and emotional challenges for both the individual and their family and friends.
- There is no cure for MS, but it has been proven that disease modifying therapies (DMTs) can have a significant impact on relapse rate and the progression of disability. There are a wide range of factors that can contribute to an individual's preference for treatment so adding cladribine to the range of DMT options available increases the opportunity for personalisation of MS treatment.
- Cladribine is administered as two short courses of tablets taken at home which offers a new way to take a treatment for MS. Oral treatments are generally preferred to injections or infusions to avoid the need to travel to a hospital clinic for treatment. Less frequent administration would also be welcomed.
- The patients that the patient groups engaged with highlighted that the short course of oral treatment, the reduced monitoring burden and reduced reliance on the health system offer significant positives for patients and their families.

Additional information: guidelines and protocols

The association of British Neurologists (ABN) published revised guidelines for the management of Multiple Sclerosis using DMTs in 2015. This guideline groups treatment options into two categories as follows:²

- Category 1: Medicines of moderate efficacy
interferons beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod
- Category 2: Medicines of high efficacy
alemtuzumab, natalizumab

For patients with more active RRMS the ABN recommends the use of category 2 medications, alemtuzumab and natalizumab.

The UK Multiple Sclerosis Society also provides guidance on the use of DMTs for patients with RRMS. With regard to the very active RRMS, in addition to alemtuzumab and natalizumab, the guidance recommends the use of fingolimod.¹³

In 2014, the National Institute for Health and Care Excellence published the Clinical Guideline CG186 for the management of MS in adults. This guideline does not provide any recommendations in relation to the use of DMTs for highly active RRMS.¹⁴

Additional information: comparators

Daclizumab, alemtuzumab, fingolimod and natalizumab.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
cladribine	3.5mg/kg bodyweight orally over 2 years	Course 1 (year 1): 28,661
		Course 2 (year 2): 28,661
daclizumab	150mg once monthly by SC injection	19,160
alemtuzumab	12mg daily for 5 days by IV infusion (course 1)	Course 1 (year 1): 35,225
	12mg daily for 3 days by IV infusion (course 2)	Course 2 (year 2): 21,135
fingolimod	500 micrograms once daily, orally	19,110
natalizumab	300mg every 4 weeks by IV infusion	13,560

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online accessed on 3 November 2017. Costs are based on a bodyweight of 70kg. Costs do not take any patient access schemes into consideration. SC: subcutaneous, IV: intravenous. Cladribine and alemtuzumab are administered as two courses (in years 1 and 2) only.

Additional information: budget impact

The submitting company estimated there would be 606 patients eligible for treatment with cladribine in years 1 to 5 to which confidential estimates of treatment uptake were applied.

The gross impact on the medicines budget was estimated to be £856k in year 1 and £1.8m in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £144k in year 1 and a saving of £168k in year 5.

The analysis also included additional savings for medicine administration. The net total budget impact was estimated to be £39k in year 1 and a saving of £466k in year 5.

These estimates do not take account of any patient access schemes applied to displaced medicines.

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

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This assessment is based on data submitted by the applicant company up to and including 12 December 2017.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

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 drug 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 NHS Scotland 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 NHS Scotland 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.