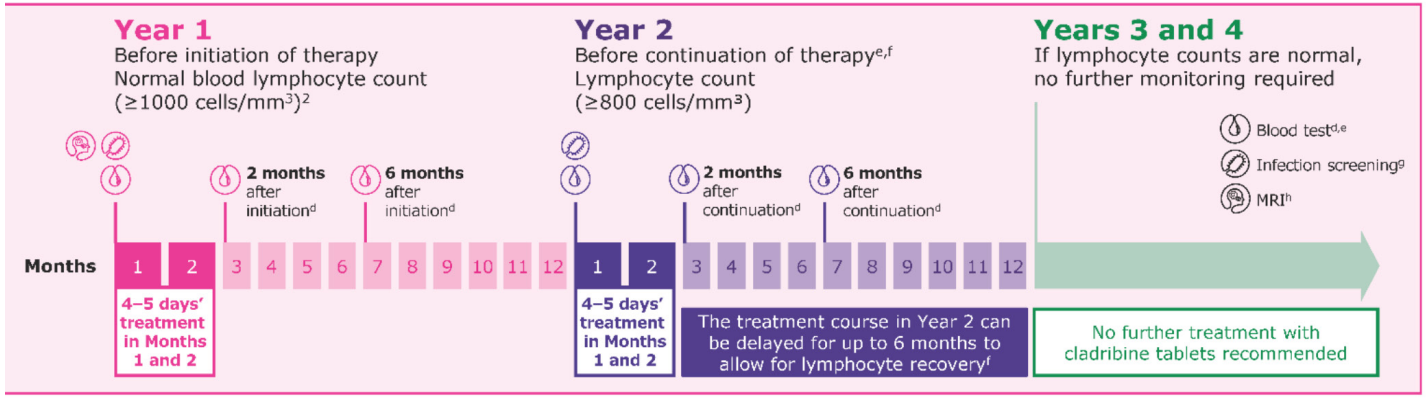
Supplemental Digital Content 1: Dosing and administration of cladribine tablets

How to take cladribine tablets[1]

Monitoring and administration of cladribine tablets over a 4-year time horizon[1]



Dosing of cladribine tablets[1]

Weight range (kg)	Total number of tablets over 2 years
40[c] to <50	**16**
50 to <60	**20**
60 to <70	**24**
70 to <80	**28**
80 to <90	**30**
90 to <100	**34**
100 to <110	**38**
≥110	**40**

The recommended cumulative dose of cladribine tablets is 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Following completion of the two treatment courses, no further treatment with cladribine tablets is required in Years 3 and 4
Serum aminotransferase, alkaline phosphatase, and total bilirubin should be obtained before initiation of therapy in Years 1 and 2.[1] During treatment, liver enzyme and bilirubin monitoring should be obtained based on clinical signs and symptoms[1]
[a]Leave a gap of at least 3 hours before or after taking cladribine tablets; [b]If a dose is missed, take it on the same day, if possible. Doses that are not remembered until the next day will add 1 day of treatment to the treatment week; [c]The use of cladribine tablets in patients weighing <40 kg has not been investigated; [d]If the lymphocyte count is <500 cells/mm³, it should be actively monitored until values increase again. If the lymphocyte count is <200 cells/mm³, antiherpes prophylaxis according to local standard practice should be considered during the time of Grade 4 lymphopenia; [e]The schedule for initiation and continuation of therapy with cladribine tablets may need to be adjusted based on absolute lymphocyte counts; [f]If recovery takes >6 months, the patient should not receive further treatment with cladribine tablets; [g]HIV infection, active tuberculosis, and active hepatitis must be excluded before treatment initiation in Years 1 and 2; [h]Baseline MRI should be performed before initiating treatment (usually within 3 months)
HIV, human immunodeficiency virus; MRI, magnetic resonance imaging

1. MAVENCLAD® [cladribine tablets] EU Summary of Product Characteristics. Accessed March 16, 2021. https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-information_en.pdf.
2. Cook S, Vermersch P, Comi G, et al. Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orally) study. *Mult Scler.* 2011;17:578–593

Supplemental Digital Content 2: Pre-screening checklist[1]

Test, Screening or Counseling	Date obtained or completed
Screenings	
Cancer – Exclude active malignancy Age and sex-appropriate cancer screening up to date	
Pregnancy – Exclude pregnancy[a]	
Immunosuppression[a] – Exclude immunocompromised status, including receiving immunosuppressive or myelosuppressive therapy (such as methotrexate, cyclophosphamide, cyclosporine or azathioprine, or chronic use of corticosteroids)	
Renal impairment (exclude moderate or severe renal impairment; creatinine clearance <60 mL/min)	
Hepatic impairment (exclude moderate or severe hepatic impairment; Child–Pugh score >6)	
Infections[a] – Rule out human immunodeficiency virus and active chronic infections (tuberculosis or hepatitis)	
Counseling	
Both men and women should be advised to use effective birth control during treatment and for 6 months after last dose[a]	
MRI	
Establish baseline	
Exclude progressive multifocal leukoencephalopathy	
Blood tests	
Complete blood count[a] – Normal lymphocyte count	
Aminotransferase, alkaline phosphatase, and total bilirubin[a]	
Immunizations and vaccinations[b]	
Varicella-zoster virus – Vaccination of antibody-negative patients	

[a]Must be performed prior to initiation of therapy in both Year 1 and Year 2; [b]The MS International Federation indicates that patients about to start cladribine tablets should consider getting fully vaccinated against COVID-19 (single dose of the J&J vaccine or the second dose of any other type of vaccine) 2–4 weeks prior to starting treatment[2]

1. MAVENCLAD® [cladribine tablets]. EU Summary of Product Characteristics. Accessed August 3, 2021. https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf
2. Multiple Sclerosis International Federation. MS, the coronavirus and vaccines – updated global advice. Accessed August 3, 2021. https://www.msif.org/news/2020/02/10/the-coronavirus-and-ms-what-you-need-to-know/

Supplemental Digital Content 3: Common questions and concerns

How will I know if the treatment is working? Will I stop having relapses entirely?

An important part of good communication between healthcare practitioners (HCPs) and patients is managing patient expectations, as misunderstanding and miscommunication can reduce patient trust.[1] Patients and HCPs may not be fully aligned when communicating about multiple sclerosis (MS) due to a difference in perspective; therefore, conversations around treatment success or failure must be individualized, with both parties actively partnering to set realistic expectations for treatment, and to determine whether agreed therapeutic goals are being met.[1] Patients who do not experience side effects may also need reassurance that a lack of adverse events does not indicate a lack of efficacy.

Another important concept to communicate is how to clearly identify relapses. Defining relapses as "new or worsening symptoms that last at least 24 hours, occur at least 30 days after the start of the last relapse and are not caused by other factors (such as heat, stress or infection)" can help patients to determine when they are having a relapse. It is important for patients to understand that relapses (and/or new magnetic resonance imaging [MRI] lesions) may develop after treatment initiation and before treatment has become fully effective; relapses could occur within the first 6 months after treatment initiation with cladribine tablets.[2]

Although the idea of "MS remission" or achieving "no evidence of disease activity" is appealing to both patients and clinicians, in practice some degree of disease activity can be picked up depending on the definition or sensitivity of measurements used. Whether these goals have been achieved often depends on how remission is defined and how long patients are followed during or after treatment. Once again, a strong partnership that fosters patient understanding is key to setting expectations.[1]

Real-world experience indicates high treatment persistence with cladribine tablets. A large cohort of 496 people with relapsing-remitting MS treated with cladribine tablets gathered from the MSBase registry found that treatment persistence was 95% in the first year.[3] The efficacy observed in these patients in terms of reducing annualized relapse rate was consistent with that in clinical trials.[3] Furthermore, post-approval safety data from more than 35,668 patients who received cladribine tablets were consistent with the safety profile of cladribine tablets in clinical trials.[4]

It is important to note that disease activity in Year 1 should not always prompt a change in treatment. One analysis found that more than half of patients who had a relapse in Year 1 were subsequently relapse-free in Year 2.[5] It is therefore important to complete the indicated treatment dosage of cladribine tablets over 2 years.

There have been different attempts to describe the desired treatment response to cladribine tablets in the literature; common to all is a reduction in clinical and MRI disease activity below baseline levels for a long follow-up period. For example, complete treatment response to cladribine tablets has been defined as "no evidence of significant clinical or radiological activity after completion of the full recommended cumulative dose."[2] Optimal response was defined as stable disease activity during the first 2 years and up to at least 4 years after starting treatment, while sustained response was defined as an ongoing lack of MS activity up to at least 5 years after treatment initiation.[6]

Significant disease activity or progression after cladribine tablets treatment likely suggests treatment failure to both the patient and HCP. Meuth et al[6] suggested that a patient with significant disease activity (a severe relapse or ≥2 relapses) or progression (by ≥1 Expanded Disabilility Status Scale point) detected 3 months into Year 1 constituted a non-responder and the patient should be switched to another highly effective disease-modifying therapy (DMT). In the same publication, the authors present different scenarios for retreating with an additional course(s) of cladribine tablets (e.g. patients with reappearing significant disease activity in Year 3 or 4); however, there are currently no studies that support such recommendations. Patients may also wish to switch treatments due to issues such as perceived lack of efficacy, tolerability, or due to inconvenience.

A desire to switch treatment should be treated similarly to any other clinical concern. The first goal is to gain a thorough understanding of the patient's symptoms and concerns as well as their point of view. Encouraging the patient to participate in the decision-making process will require explanation of how treatment decisions are informed by both severity and timing of disease activity relative to dosing. Being as transparent as possible while gauging the patient's understanding is key to patient satisfaction with both the clinician and the care received.

The patient asks what happens if this treatment does not work for them.

What will we do if I do have a relapse?

Patients need to know what actions to take when symptoms are observed. They are likely to reach out to their MS nursing team or their general practitioner when encountering concerning symptoms and may need to be evaluated to determine whether they are experiencing disease activity and/or side effects of treatment.

The patient should also be reassured that a relapse in the first year after treatment does not necessarily mean that there will be more relapses in subsequent years. If there is relapse activity in the second year of treatment, disease activity should be compared to baseline (before treatment with cladribine tablets). If there has been a reduction in disease activity, further assessment may be warranted before considering switching treatment. Similarly, relapse during the third or fourth years after initial treatment requires comparison to baseline disease status. An initial treatment response followed by new disease activity could indicate a need for a different treatment approach. Although the EU Summary of Product Characteristics for cladribine tablets does not specify how patients should be treated after the end of 4 years, there is no contraindication to retreatment if warranted by the patient's clinical presentation or MRI scans.[7]

How might I feel after treatment? Will the treatment make me sick?

As patients may prioritize their quality of life over preventing relapses to a greater extent than their HCP, it is important to discuss

some of the likely adverse events (AEs) in the context of shared decision-making.[1] Educating patients regarding possible side effects fosters co-ownership of their treatment plan and helps to encourage treatment adherence.[8]

Early in treatment, patients should be advised that the most common treatment-emergent AEs observed in people with MS within the first 6 months after treatment with cladribine tablets were headache, lymphopenia and nasopharyngitis (*Figure 2*).[9] Based on pooled analyses of clinical studies, lymphopenia is considered very common (experienced by an average of 1 or more patients out of every 10).[7] Oral herpes, dermatomal herpes zoster, decreased neutrophil count, rash and alopecia are considered common AEs (≥1% but less than 10% of patients).[7]

In addition to knowing what to expect based on clinical study data, patients may find it reassuring if HCPs share their experiences based on the AEs that their patients have reported, how they have tolerated treatment and how many of their patients have remained on cladribine tablets treatment.

If this treatment does not work, are there alternatives?

For any treatment, if response is suboptimal, patients should be offered alternatives. However, the decision to switch medications should consider both the possible benefits as well as the potential risk.[2]

Data on switching from cladribine tablets to another treatment are limited.[10,11] Expert opinion does not exclude particular treatments after cladribine tablets but recommends considering individual patient circumstances, including potential additive effects on the immune system and the clinical need that is driving the treatment switch.[2] It should be noted, however, that a study of patients treated with cladribine tablets who had previously received treatment with natalizumab found evidence of treatment efficacy without evidence of additive negative effects.[12] Generally, no safety interval is needed when switching from cladribine tablets to glatiramer acetate, interferon-beta or dimethyl fumarate, while 4 weeks are required for teriflunomide or fingolimod, 4–8 weeks for natalizumab and 6–12 months for switching to alemtuzumab or ocrelizumab.[2]

The patient asks what will happen if they want to start a family in the future.

How does this treatment affect my ability to start a family?

Women of childbearing potential and males who could potentially father a child must take precautions to prevent pregnancy during treatment and for 6 months after each treatment course. The recommended dosing of cladribine tablets is over 2 years, with each treatment course consisting of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month in each of the respective treatment years (*Supplemental Digital Content 1*).[7] It is important to discuss pregnancy prevention and include information on contraception with all patients of childbearing age before treatment initiation, including using an additional barrier method if oral contraceptive pills are used for contraception.[7] If pregnancy does occur within 6 months after the last dose, patients should be advised of the potential risks to the fetus and referred to a high-risk pregnancy clinic.[2] People with MS should avoid breastfeeding during treatment with cladribine tablets and for 1 week after each dose.[7]

If I only take this for a few days, how long does it last?

The extremely short course of treatment may provide benefits in terms of patient convenience and adherence. However, it may also cause concerns that efficacy will be transient. It may be beneficial to explain to the patient that the short course of treatment produces long-term beneficial changes to their immune system, and that the current data support the long-term efficacy of cladribine tablets. In addition to the efficacy observed in the first 4 years after treatment initiation, longer-term studies are becoming available. Interim analysis of the long-term CLASSIC-MS study found minimal increases in disability and that most patients did not require further treatment with DMTs (*Figure 1b*).[11] Patients should also be reassured that the option to switch to a different treatment is available if efficacy is not observed even after a full course of treatment with cladribine tablets.

How did other patients feel with this treatment?

MS nurses can take this opportunity to share their observations about treatment with cladribine tablets in their own patients. Although some patients have reported fatigue in the early weeks, generally people with MS treated with cladribine tablets have reported improved quality of life compared with placebo.[13]

Can I get vaccinated while taking this treatment?

The COVID-19 pandemic and subsequent vaccine development and availability have increased patient interest and concern regarding all vaccines. It is important to note that none of the COVID-19 vaccines available at the time of writing are either live or live-attenuated vaccines. A study that examined immune response to the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine in patients with MS found that MS patients treated with cladribine tablets demonstrated an antibody response similar to untreated people with MS and to healthy subjects.[14] Similar results were found for patients being treated with cladribine tablets who were vaccinated against seasonal influenza and varicella-zoster virus (VZV).[15,16]

Use of live or live-attenuated vaccines should be avoided during treatment with cladribine tablets and delayed until the patient's white blood cell counts are within normal limits.[7] In addition to this guidance, recommendations have been provided per expert opinion; for certain multidose vaccinations (such as hepatitis B, human papillomavirus, VZV, measles and pneumococcus), clinicians may consider giving the first dose 4–6 weeks before treatment initiation and give subsequent doses after treatment initiation when lymphocyte counts have recovered.[2]

Do I have to change my treatment due to the pandemic?

COVID-19 has become a serious health concern throughout the world. Despite safety concerns due to the pandemic, monitoring disease activity remains crucial for MS treatment. In-person consultations are generally preferable, but strategies that may help keep patients in touch with their clinicians include phone consultations/telemedicine, virtual monitoring/consultations and self-reported symptoms through methods such as Clinic Speak. Video appointments are generally preferable to phone consultations as they allow the HCP to establish a rapport with the patient and may help them pick up on non-verbal cues.

Although data are limited, in practice, patients with MS treated with cladribine tablets who contract COVID-19 do not seem to have a more serious course of illness than those not receiving cladribine tablets.[17] In

addition, it has been shown that patients receiving cladribine tablets are able to develop anti-SARS-CoV-2 antibodies, notwithstanding low lymphocyte levels.[4,18–20]

Patients with MS should be advised not to alter or discontinue their DMT.[21,22] Although treatment decisions must always be made on an individual basis, given the particular concerns around COVID-19 and DMT, any treatment decisions need to be made in partnership with their treating clinician while taking into account the patient's unique situation.[21,22] It is worthwhile to mention the long-term risk to an MS patient who does not take their prescribed MS therapy, due to an increased chance of subsequent relapse and the potential for increased disability progression. Any change in treatment should be closely reviewed with the treating physician and their team.

1. Celius EG, Thompson H, Pontaga M, et al. Disease progression in multiple sclerosis: a literature review exploring patient perspectives. *Patient Prefer Adherence.* 2021;15:15–27.
2. Sørensen PS, Centonze D, Giovannoni G, et al. Expert opinion on the use of cladribine tablets in clinical practice. *Ther Adv Neurol Disord.* 2020;13:1756286420935019.
3. Butzkueven H, Spelman T, Hodgkinson S, et al. Real-world experience with cladribine tablets in the MSBase registry (2942). Paper presented at: 73rd Annual Meeting of the American Academy of Neurology; April 17–22, 2021; Virtual.
4. Giovannoni G, Berger J, Leist T, et al. Post-approval safety of cladribine tablets with particular reference to COVID-19 outcomes: an update. Paper presented at: 7th ACTRIMS Forum; February 24–26, 2022; Virtual.
5. Yamout B, Giovannoni G, Magyari M, et al. Preservation of relapse-free status in year 2 of treatment with cladribine tablets by relapse-free status in year 1. Paper presented at: 6th Congress of the European Academy of Neurology; May 23–26, 2020; Virtual.
6. Meuth SG, Bayas A, Kallmann B, et al. Long-term management of multiple sclerosis patients treated with cladribine tablets: an expert opinion. *Expert Opin Pharmacother.* 2020;21(16):1965–1969.
7. MAVENCLAD® [cladribine tablets]. EU Summary of Product Characteristics. Accessed March 16, 2021. https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf
8. Frankel RM, Stein T. Getting the most out of the clinical encounter: the four habits model. *J Med Pract Manage.* 2001;16(4):184–191.
9. Brochet B, Hupperts R, Langdon D, et al. Treatment satisfaction in patients with highly-active relapsing multiple sclerosis treated with cladribine tablets: CLARIFY-MS study interim analysis. Paper presented at: 8th Joint ACTRIMS-ECTRIMS Congress; September 11–13, 2020; Virtual.
10. Patti F, Visconti A, Capacchione A, Roy S, Trojano M. Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS). *Ther Adv Neurol Disord.* 2020;13:1756286420922685.
11. Giovannoni G, Leist T, Aydemir A, Verdun di Cantogno E. CLASSIC-MS: long-term efficacy and real-world treatment patterns for patients receiving cladribine tablets - interim data with 8–14 years' follow-up. Paper presented at: 8th Joint ACTRIMS-ECTRIMS Congress; September 11–13, 2020; Virtual.
12. Möhn N, Skripuletz T, Sühs KW, Menck S, Voss E, Stangel M. Therapy with cladribine is efficient and safe in patients previously treated with natalizumab. *Ther Adv Neurol Disord.* 2019;12:1756286419887596.
13. Afolabi D, Albor C, Zalewski L, Altmann DR, Baker D, Schmierer K. Positive impact of cladribine on quality of life in people with relapsing multiple sclerosis. *Mult Scler.* 2018;24(11):1461–1468.
14. Achiron A, Mandel M, Dreyer-Alster S, et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. *Ther Adv Neurol Disord.* 2021;14:17562864211012835.
15. Roy S, Boschert U. Analysis of influenza and varicella zoster virus vaccine antibody titers in patients with relapsing multiple sclerosis treated with cladribine tablets. Paper presented at: Annual Forum of the Americas Committee for Treatment and Research in Multiple Sclerosis; February 25–27, 2021; Virtual.
16. Wu GF, Boschert U, Hayward B, Lebson LA, Cross AH. Evaluating the impact of cladribine tablets on the development of antibody titers: interim results from the CLOCK-MS influenza vaccine substudy. Paper presented at: Annual Forum of the Americas Committee for Treatment and Research in Multiple Sclerosis; February 25–27, 2021; Virtual.
17. Jack D, Damian D, Nolting A, Galazka A. COVID-19 in patients with multiple sclerosis treated with cladribine tablets: an update. *Mult Scler Relat Disord*. 2021;51:102929.
18. Oreja-Guevara C, Meca-Lallana V, Brieva L, et al. COVID-19 in cladribine-treated patients with multiple sclerosis. Paper presented at: 8th Joint ACTRIMS-ECTRIMS Congress; September 11–13, 2020; Virtual.
19. De Angelis M, Petracca M, Lanzillo R, Brescia Morra V, Moccia M. Mild or no COVID-19 symptoms in cladribine-treated multiple sclerosis: two cases and implications for clinical practice. *Mult Scler Relat Disord*. 2020;45:102452.
20. Celius EG. Normal antibody response after COVID-19 during treatment with cladribine. *Mult Scler Relat Disord.* 2020;46:102476.
21. National Multiple Sclerosis Society. MS treatment guidelines during coronavirus. Accessed May 12, 2021. https://www.nationalmssociety.org
22. Multiple Sclerosis International Federation. Global COVID-19 advice for people with MS. Accessed May 12, 2021. https://www.msif.org

Supplemental Digital Content 4: Responses to commonly asked questions

Do cladribine tablets increase the risk of cancer?

Data from the original clinical trials indicated the potential for a greater incidence of malignancies in people with MS treated with cladribine tablets.[1,2] However, this may have been due to unexpectedly low rates of malignancies in patients given placebo in those clinical trials.[2] Subsequent epidemiologic analyses found similar rates of malignancies in patients treated with cladribine tablets compared to a reference population (i.e. background levels).[3,4]

Are there other treatments that may work if cladribine tablets do not?

Yes. Other types of treatments may be beneficial if cladribine tablets do not work for you.

What does it mean if I experience a relapse while taking cladribine tablets?

Relapses may occur—especially very early in treatment—but this does not necessarily mean that the treatment has not worked. If the relapses persist or other symptoms or MRI results worsen during or after treatment, a switch to another treatment may be considered.

1. MAVENCLAD® [cladribine tablets]. EU Summary of Product Characteristics. Accessed March 16, 2021. https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf
2. Cook S, Vermersch P, Comi G, et al. Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study. *Mult Scler.* 2011;17(5):578–593.
3. Cook S, Leist T, Comi G, et al. Safety of cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis. *Mult Scler Relat Disord.* 2019;29:157–167.
4. Leist T, Cook S, Comi G, et al. Long-term safety data from the cladribine tablets clinical development program in multiple sclerosis. *Mult Scler Relat Disord*. 2020;46:102572.