Cladribine as Exit Therapy in Aging RMS Patients: Therapeutic Assessment and Method Validation Review"

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ABSTRACT

As the number of older individuals with relapsing multiple sclerosis (RMS) grows, managing treatment becomes more complex due to reduced DMT effectiveness and higher risks of infections and comorbidities. Cladribine tablets (CladT), an immune reconstitution therapy, offer a potential “exit strategy” by providing long-lasting disease control after two short annual treatment courses. Evidence suggests CladT remains effective regardless of age, with no significant age-related safety concerns reported so far. However, elderly patients may still face a higher infection risk due to immunosenescence, so vaccinations (e.g., pneumococcal, herpes zoster) are advised. CladT may be a suitable option for older patients with RMS seeking to avoid continuous immunosuppression. Also, this article provides information about method validation of cladribine

Keywords: Cladribine tablets; Relapsing multiple sclerosis; Disease-modifying therapy; Ageing, method validation

INTRODUCTION

Currently, there is no cure for MS. Treatment strategies focus on reducing the frequency of relapses and slowing the progression of disability. [2] The disease presents a wide range of symptoms and varies significantly among individuals, making it challenging to directly compare the effectiveness of different treatments.

In recent years, the number of disease-modifying therapies (DMTs) for MS has expanded. Many of these treatments require continuous administration and regular monitoring, which can be burdensome for patients and may affect adherence to the therapy regimen.

Cladribine tablets have emerged as a high-efficacy oral treatment option for patients with relapsing forms of MS. The treatment involves two short courses over two years, with no additional dosing required in the subsequent two years. This dosing schedule offers a less intensive treatment regimen compared to other DMTs, potentially improving patient adherence and quality of life.[3]

Clinical studies have demonstrated that cladribine tablets effectively reduce relapse rates and slow disease progression, with a favourable safety profile. The convenience of oral administration and the reduced need for ongoing monitoring make cladribine a compelling option for many patients with MS.

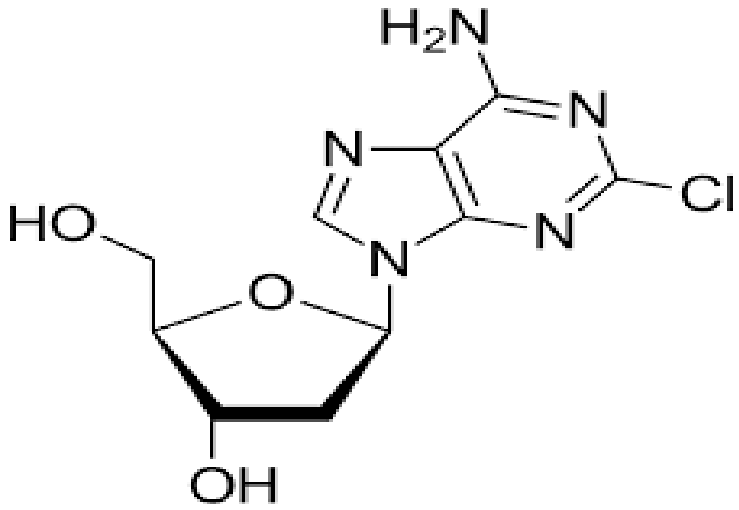
In summary, while MS remains an incurable condition, advancements in treatment options like cladribine tablets offer promising avenues for managing the disease more effectively and with greater convenience for patients.[4]

Introduction to cladribine [5]

Cladribine is a synthetic purine nucleoside analogue and a chlorinated derivative of the naturally occurring base, adenine. It functions primarily by inducing apoptosis (programmed cell death) in both B and T lymphocytes, which are key immune cells involved in the inflammatory processes associated with multiple sclerosis (MS). Through this mechanism, cladribine helps to suppress the abnormal immune activity that damages the protective myelin sheath in the central nervous system.

Originally developed for use in oncology, cladribine was first approved by the U.S. Food and Drug Administration (FDA) in 1993 for the treatment of haematological cancers, especially certain types of leukaemia. One of its primary indications remains hairy cell leukaemia, a rare but chronic form of blood cancer, for which it is still widely prescribed.

In more recent years, the therapeutic scope of cladribine has expanded. The European Medicines Agency (EMA) approved cladribine tablets for the treatment of relapsing forms of multiple sclerosis in 2017, recognizing its ability to modulate the immune system with limited dosing. This was followed by FDA approval in the United States in 2019, marking its official inclusion in the portfolio of disease-modifying therapies for MS. This expansion of its use reflects growing confidence in its effectiveness and safety profile for autoimmune neurological conditions beyond its original use in cancer.



Mechanism of action [6,7]

Cladribine is a purine nucleoside analogue, structurally similar to deoxyadenosine. It is used as a disease-modifying therapy in multiple sclerosis (MS) and as a chemotherapeutic agent in hematologic malignancies like hairy cell leukaemia. Its mechanism of action involves selective lymphocyte depletion, primarily affecting B and T lymphocytes, making it effective in autoimmune conditions like MS.

Detailed Mechanism of Action:

1. Prodrug Activation:
    - Cladribine (2-chlorodeoxyadenosine) enters cells and is phosphorylated by deoxycytidine kinase (dCK) into its active form: → Cladribine → 2-CdAMP → 2-CdATP (active triphosphate).
    - dCK is more active in lymphocytes than other cells, making lymphocytes especially susceptible.
2. Intracellular Accumulation:
    - In cells with low 5'-nucleotidase activity (like lymphocytes), 2-CdATP accumulates.
    - This imbalance leads to disruption of nucleotide pools, DNA strand breaks, and inhibition of DNA repair mechanisms.

 Incorporation into DNA:

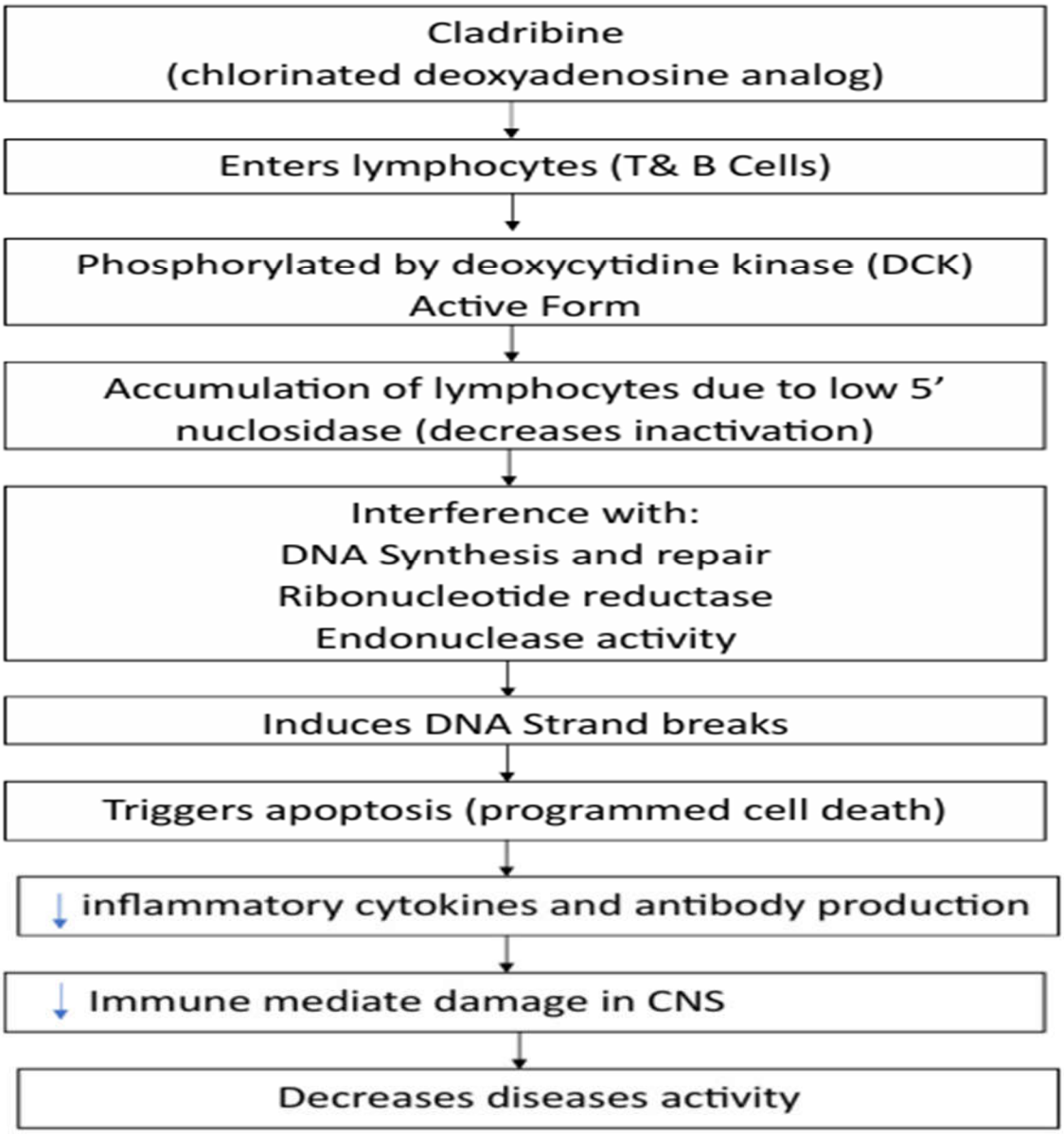
- 2-CdATP is incorporated into DNA during replication.
- Causes single- and double-strand breaks, triggering apoptosis (programmed cell death).

 Selective Cytotoxicity:

- Cladribine targets dividing and non-dividing lymphocytes:
    - B cells: Rapidly and profoundly depleted.

- T cells: Also affected, but more slowly and less deeply.

- Monocytes, neutrophils, and other cells are relatively spared due to their different dCK/5'-nucleotidase ratios.



Induction Therapy and Re-dosing with Cladribine Tablets

Induction therapy typically involves administering potent immunosuppressive agents early in treatment, followed by a maintenance phase using immunomodulatory drugs. However, cladribine tablets, as per current approval, are not classified as induction therapy, since most patients maintain remission for up to four years or longer after treatment. Cladribine functions as an immune reconstitution therapy (IRT), initially causing lymphocyte depletion, which is subsequently followed by the regeneration of naive lymphocyte populations.[8]

Before starting treatment, patients should undergo a comprehensive baseline evaluation, as outlined in the treatment protocol (refer to Figure 1). It is essential to assess disease activity and risk on an individual basis, considering the patient's personal lifestyle preferences and treatment goals.

Monitoring disease activity during cladribine therapy depends on when and how the disease manifests. For instance, if disease activity is observed in the second year, following completion of the second treatment course, re-treatment is not advised according to current guidelines. Nevertheless, given the underlying immunopathology of multiple sclerosis and cladribine's IRT mechanism, re-treatment may be a viable option, much like the current clinical approach with alemtuzumab. At present, there is no clinical evidence available to support restarting cladribine therapy after Year 4.[9]

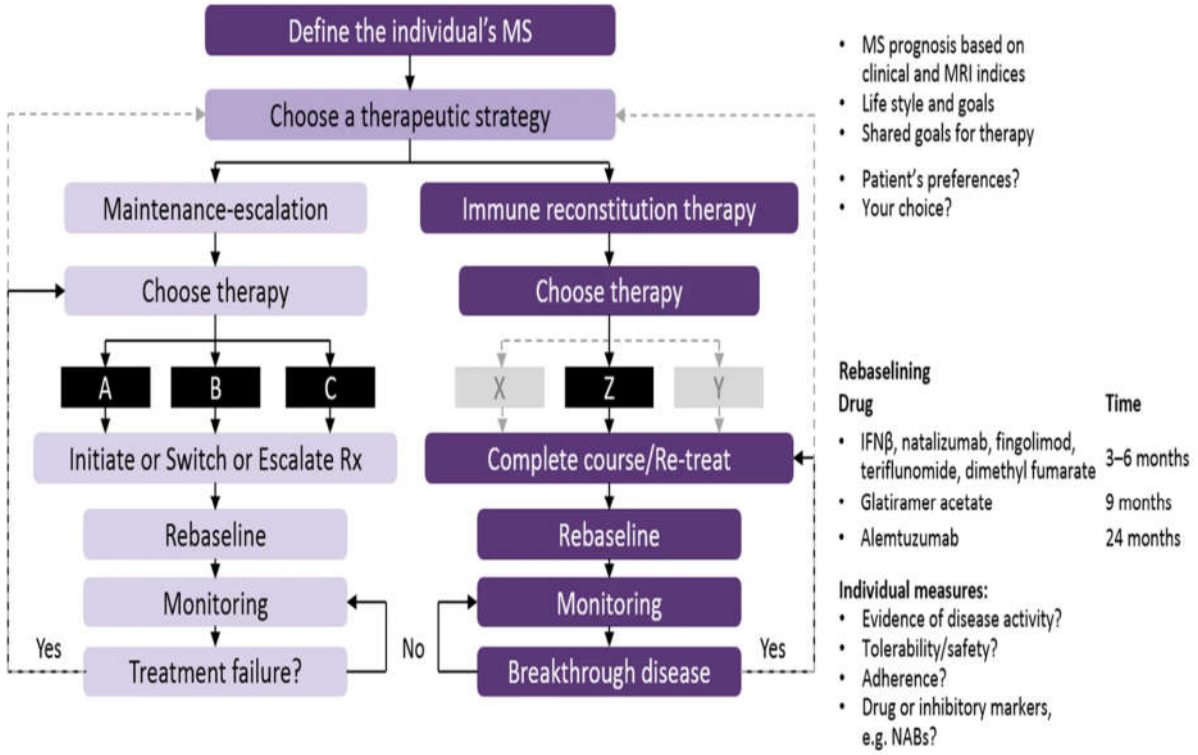


Figure 1: Treat-2-target algorithm of NEDA in relapsing forms of MS (adapted from Giovannoni et al.

Cladribine Tablets and the Cost of Managing Patients with MS

Multiple sclerosis (MS) places a significant financial strain on healthcare systems, with increasing expenditures related to disease-modifying therapies (DMTs) and the necessary monitoring. [10,11] The introduction of intravenous DMTs administered in hospital settings has led to greater use of healthcare resources for both treatment delivery and patient oversight. A simulation study conducted in the UK from a healthcare facility standpoint suggested that cladribine tablets may help reduce the need for hospital-based administration and monitoring. [12] Despite this, the cost of DMTs remains a key factor in economic evaluations. Nonetheless, cladribine tablets have demonstrated cost-effectiveness when compared with other therapies in various country-specific health economic models. It includes Finland [13], Portugal [14], Spain [15], Saudi Arabia [16], Chile [17], Iran [18], and Poland [19].

Lymphopenia and Infections (numbering karvana baki)

Cladribine tablets (CladT), marketed as MAVENCLAD®, are an oral disease-modifying therapy for relapsing multiple sclerosis (RMS). They function as an immune reconstitution therapy, leading to a significant reduction in B lymphocytes and a moderate reduction in T lymphocytes.

Lymphocyte Reduction and Recovery

CladT induces a marked decrease in B lymphocytes, with the lowest levels (nadir) typically occurring several months post-treatment. Recovery of B cells generally occurs over approximately 30 weeks after the second treatment course. T lymphocytes experience a less pronounced reduction, with nadirs occurring slightly later and recovery spanning about 43 weeks post-treatment.

Lymphopenia and Management

Lymphopenia, a reduction in lymphocyte count, is a recognized side effect of CladT. Severe cases (Grade 3 or 4) are uncommon, particularly when the absolute lymphocyte count (ALC) is allowed to recover to at least 800 cells/mm³ before initiating the second annual treatment course. Monitoring ALC and adjusting treatment schedules accordingly can mitigate the risk of severe lymphopenia.

Safety Considerations

Although CladT is typically well-tolerated, it is important to assess patients for existing infections—such as tuberculosis and varicella zoster—before starting treatment. Postponing the second course of therapy until lymphocyte levels have sufficiently recovered can help lower the risk of infections linked to reduced lymphocyte counts.
Overall, CladT leads to a significant but manageable reduction in both B and T cells, with a consistent pattern of immune cell recovery. Following established monitoring protocols and treatment recommendations helps to limit the occurrence of serious lymphopenia and its potential complications. [20,21]

Contraindications

Cladribine should not be used by individuals with multiple sclerosis who have conditions such as liver cirrhosis, chronic kidney disease, active cancer, HIV infection, or tuberculosis. It is also contraindicated in patients with a prior history of treatment using other immunosuppressive agents like cyclophosphamide, azathioprine, methotrexate, or mitoxantrone. Because cladribine may harm fetal development and affect sperm health, both men and women who are sexually active should receive thorough counseling on these reproductive risks. It is essential that patients follow strict contraceptive measures before starting treatment, throughout the course of therapy, and for a period afterward. Additionally, cladribine has not been studied in individuals under 18 years of age, and its use is not recommended in this age group.[22]

Monitoring

Before initiating oral cladribine as a disease-modifying treatment for multiple sclerosis, several laboratory evaluations are necessary. These include a complete blood count with differential, a comprehensive metabolic panel, screening tests for HIV and viral hepatitis, a pregnancy test, and an interferon-gamma release assay (QuantiFERON-TB) to check for latent tuberculosis. It is also important to thoroughly review the patient's current and past medications, as cladribine should not be used alongside other immunosuppressive therapies. After beginning cladribine, patients should have their complete blood count with differential monitored at approximately 3 and 7 months after each treatment course, during the 2-year treatment period. If the therapy is well-tolerated, continued routine blood monitoring may not be needed beyond those initial two years.

Method development and validation of cladribine Tablets

Title	Method	PARAMETERS	Ref.
Development and validation of a sensitive and specific hplc assay of cladribine for pharmacokinetics studies in rats *	HPLC	**Stationary Phase**: Shimadzu LC-9A pump, a 3 µm, 250 x 2.0 mm I.D. high speed C18 column (Jupiter®), preceded by a 5 µm 4 x 4 mm I.D. C18 guard column (Licrocart®), an Agilent Model 1050 UV-VIS detector and a 3395 Integrator **Mobile Phase**: 0.01M KH2PO4 (pH 5): methanol: acetonitrile (90:5:5). **flow rate:** 0.3 mL/min **UV wavelength**: 265 nm	23
Performing a physiologically relevant test for cladribine tablets	HPLC	**Stationary Phase** – Grace HPLC Column Platinum C18-EPS, 250 × 4.6 mm, 5 mm **mobile phase** A – 0.1 % H3 PO4 solution, phase B – acetonitrile. **Flow Rate**: 0.5 ml/min **UV Wavelength**: 252 nm	24
Rp-Hplc method for the quantification of cladribine in pharmaceutical formulation	HPLC	**Stationary Phase**: Zodiac C18 (250x4.6mm, 5µm in particle size **Mobile phase**: Methanol: Acetonitrile: Water in the ratio of 64:22:14%, v/v/v **flow rate** :1ml/min **UV Wavelength**: 231 nm	25

Conclusion

Cladribine tablets may serve as an effective "exit therapy" for older patients with stable multiple sclerosis by offering lasting disease control with limited long-term treatment. Due to its short treatment course and manageable safety profile, cladribine can reduce the need for continuous therapy and monitoring, making it a suitable option for elderly patients who are stable and wish to discontinue more intensive treatments.

References

[1] The Multiple Sclerosis International Federation. Atlas of MS 3rd edn. 2020. https://www.msif.org/ wp-content/uploads/2020/12/Atlas-3rd-EditionEpidemiology-report-EN-updated-30-9-20.

[2] Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler. 2018;24(2):96–120.

[3] Giovannoni G. Disease-modifying treatments for early and advanced multiple sclerosis: a new treatment paradigm. Curr Opin Neurol. 2018;31(3): 233–43.

[4] Boyko AN, Boyko OV. Cladribine tablets' potential role as a key example of selective immune reconstitution therapy in multiple sclerosis. Degener Neurol Neuromuscular Dis. 2018;8:35–44.

[5] FDA Approved Drug Products: MAVENCLAD (cladribine) tablets, for oral use (December 2023)

[6] Janiec K, Wajgt A, Kondera-Anasz Z. Effect of immunosuppressive cladribine treatment on serum leucocytes system in two-year clinical trial in patients with chronic progressive multiple sclerosis. Med Sci Monit. 2001 Jan-Feb;7(1):93-8. [PubMed]

[7] Niezgoda A, Losy J, Mehta PD. Effect of cladribine treatment on beta-2 microglobulin and soluble intercellular adhesion molecule 1 (ICAM-1) in patients with multiple sclerosis. Folia Morphol (Warsz). 2001 Aug;60(3):225-8. [PubMed]

[8] Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? Mult Scler Relat Disord. 2015;4(4):329–33.

[9] Merck Serono Ltd. MAVENCLAD 10 mg tablets summary of product characteristics. https://www. medicines.org.uk/emc/product/8435. Accessed Oct 2021.

[10] Elsisi Z, Hincapie AL, Guo JJ. Expenditure, utiliza tion, and cost of specialty drugs for multiple scle rosis in the US Medicaid population, 2008–2018. Am Health Drug Benefits. 2020;13(2):74–84.

[11] Goudarzi MH, Eadie MJ, Hollingworth SA. Disease modifying therapies for relapsing-remitting multi ple sclerosis: use and costs in Australia (1996–2019). Mult Scler Relat Disord. 2021; 50:102835.

[12] Tafazzoli A, Chavan A, Harty G, Moller J, Wong SL. Efficiency model of cladribine tablets versus infu sion-based disease-modifying drugs for patients with relapsing-remitting multiple sclerosis. Adv Ther. 2020;37(9):3791–806.

[13] Mankinen P, Lundstro¨m T, Soini E, et al. Cost assessment modelling of treatments for highly active relapsing multiple sclerosis. Adv Ther. 2020;37(2):800–18.

[14] Pinheiro B, Guerreiro R, Costa J, Miguel LS. Cost effectiveness of cladribine tablets versus fingolimod in patients with highly active relapsing multiple sclerosis in Portugal. J Med Econ. 2020;23(5): 484–91.

[15] Poveda JL, Trillo JL, Rubio-Terre´s C, Rubio-Rodrı´ guez D, Polanco A, Torres C. Cost-effectiveness of cladribine tablets and fingolimod in the treatment of relapsing multiple sclerosis with high disease activity in Spain. Expert Rev Pharmacoecon Out comes Res. 2020;20(3):295–303.

[16] Bohlega S, Elboghdady A, Al-Johani A, et al. Eco nomic evaluation of cladribine tablets in patients with high disease activity-relapsing-remitting mul tiple sclerosis in the Kingdom of Saudi Arabia. Value Health Reg Issues. 2021;25:189–95.

[17] Espinoza MA, Rojas R, Zaupa A, Balmaceda C. A model-based economic evaluation of cladribine versus alemtuzumab, ocrelizumab and natalizumab for the treatment of relapsing-remitting multiple sclerosis with high disease activity in Chile. Phar macoecon Open. 2021;5:635–47.

[18] Ayati N, Fleifel L, Sharifi S, Sahraian MA, Nikfar S. Cladribine tablets are a cost-effective and cost-sav ing treatment strategy for high disease activity relapsing multiple sclerosis patients in Iran. Mult Scler. 2021;27(1S):P160.

[19] Zieba P, Pawlik D, Wieczorek J, Wojcik R, Kaczor MP. Cladribine tablets (CT) versus other disease modifying therapies in the treatment of relapsing remitting multiple sclerosis (RRMS)—cost-effective ness analysis. Value Health. 2020;23(Suppl 2): PND51.

[20] Comi G, Cook S, Giovannoni G, et al. Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis. Mult Scler Relat Disord. 2019;29: 168–74.

[21] Clavelou P, Castelnovo G, Pourcher V, et al. Expert narrative review of the safety of cladribine tablets for the management of relapsing multiple sclerosis. Neurol Ther. 2023;12:1457–76.

[22] Rommer PS, Zettl UK. Managing the side effects of multiple sclerosis therapy: pharmacotherapy options for patients. Expert Opin Pharmacother. 2018 Apr;19(5):483-498.

[23] Yeung PK, Ferguson C, Jarrar A, King B, Li ML. Development and validation of a sensitive and specific HPLC assay of cladribine for pharmacokinetics studies in rats. J. Pharm. Pharm. Sci. 2007 Jan 1;10(2):231-6.

[24] Losenkova PA, Gvozdev DD, Suvorova AV, Medvedev YV, Shcherbakova VS, Kazaishvili YG, Zaslavskaya KY, Poluyanov AM, Shohin IE. Performing a physiologically relevant test for cladribine tablets.

[25] Coates LJ, Lam SC, Gooley AA, Haddad PR, Paull B, Wirth HJ. Modular, cost-effective, and portable capillary gradient liquid chromatography system for on-site analysis. Journal of Chromatography A. 2020 Aug 30; 1626:461374.