

# EXPERT OPINION ON COVID-19 VACCINATION AND THE USE OF CLADRIBINE TABLETS IN CLINICAL PRACTICE

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## CONCLUSIONS

- The responses to the questions posed in this expert opinion program are expected to cover the most important and regularly addressed aspects of COVID-19 vaccination for patients with multiple sclerosis (MS) taking cladribine tablets.
- These recommendations were developed to provide timely guidance given the sparsity of published data on COVID-19 vaccination in people with MS receiving cladribine tablets, and to reflect the knowledge, evidence, and opinion in 2021.
- One of the limitations of the consensus was the paucity of SARS-CoV-2 vaccination

data in people with MS available at the time of discussion. Recent cohort studies have identified near-normal immunoglobulin responses in patients receiving cladribine tablets, irrespective of timing and lymphocyte counts.<sup>[1-3]</sup>

- This expert opinion is expected to be a concise and thorough resource for medical professionals, with the aim of assisting them in making informed decisions regarding COVID-19 vaccinations in this group of patients to improve their standard of care.



## INTRODUCTION

- The COVID-19 pandemic has represented a global public-health emergency, which has affected both acute and ongoing medical care.
- The provision of health and social-care services for MS have been significantly affected by the COVID-19 pandemic, leading to treatment delays and interruptions to rehabilitation services.
  - In some parts of the world this has affected the health and wellbeing of people with MS, including the risk of disease progression.<sup>[4-7]</sup>
- Approved vaccines have demonstrated high effectiveness and acceptable safety in the general population, however, hesitation to be vaccinated against COVID-19 remains a challenge in some people with MS.<sup>[8,9]</sup>
- Cladribine tablets are a short-course, oral disease-modifying therapy (DMT) for use in MS; it is a deoxyadenosine analogue that selectively reduces B and T lymphocytes and is thought to interrupt the cascade of immune events central to the pathogenesis of MS.<sup>[10,11]</sup>
- All DMTs used in the treatment of MS lack vaccine-specific studies for SARS-CoV-2 due to its novel nature, although vaccine studies exist for other pathogens.



## METHODS

- The consensus program, based on a modified Delphi methodology, took place between February and May 2021.<sup>[12]</sup>
- A steering committee (SC) of 10 international MS experts led the program and developed seven clinical questions to be addressed.
- A comprehensive literature review was performed using the Population, Intervention, Comparison, Outcome (PICO) framework for each of the seven questions.

- To answer the questions, the SC developed 13 clinical recommendations, which were supported by the outcomes of the literature review.
  - The level of evidence was assessed and agreed by the SC using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) level of evidence ratings scale.<sup>[13]</sup>
- A total of 82 experts from 27 countries were invited to be part of the extended faculty (EF) and vote on the consensus recommendations (CRs). The final EF comprised 28 international experts from 19 countries (a participation rate of 34%).
- Clinical recommendations were voted on by the SC and EF members (N=38).



## RESULTS

- In total, 13 recommendations were drafted by the SC for voting. Consensus was achieved when  $\geq 75\%$  of respondents agreed in the range of 7-9 (on a 9-point scale). Consensus was achieved on all 13 of these recommendations.
- The clinical questions and recommendations are provided in Tables 1-3.

**Table 1. Consensus recommendations to address clinical questions on patient selection for COVID-19 vaccination**

**Q1. Should all people with MS receiving cladribine tablets be vaccinated against COVID-19?** (Level of evidence: high for the general population; low for specific population of people with MS being treated with cladribine tablets)

Consensus recommendation	Strength of recommendation <sup>a</sup>	Level of consensus <sup>b</sup>
<b>CR1:</b> All people with MS being treated with cladribine tablets should be vaccinated against COVID-19 as soon as possible, unless they have a contraindication	9 (8.8)	100% N=38/38
<b>CR2:</b> In general, people with MS are not more likely to contract COVID-19 or to experience a more-severe COVID-19 course. However, limited data suggest that patients on some MS therapies are at risk of more severe COVID-19 outcomes. - Early data suggest that people with MS receiving cladribine tablets are generally not at greater risk of serious disease and/or a severe outcome from COVID-19 compared with the general population and other people with MS who acquired COVID-19.	8 (7.9)	94.7% N=36/38
<b>CR3:</b> People with MS receiving treatment with cladribine tablets who have already experienced infection with SARS-CoV-2 should still be vaccinated, according to their national guidelines, after resolution of COVID-19 symptoms.	9 (8.4)	92.1% N=35/38

**Q2. Should people with MS treated with cladribine tablets be prioritized for COVID-19 vaccination? (Level of evidence: high; risk-factor subgroups are well reported in the literature)**

<b>CR4:</b> People with MS should be prioritized for COVID-19 vaccination on an individual basis depending on risk factors, including disability, age, comorbidities that increase the risk of a severe COVID-19 course, and whether they are about to start treatment with cladribine tablets.	9 (8.3)	97.4% N=37/38
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**Table 2. Consensus recommendations to address clinical questions on timing and efficacy of COVID-19 vaccination**

**Q3. Should all people with MS on cladribine tablets receive a vaccination against COVID-19 at the time it is offered? (Level of evidence: moderate)**

<b>CR5:</b> The risks of COVID-19 outweigh the risks of vaccination in people with MS who are being treated with cladribine tablets.	9 (8.7)	100% N=38/38
<b>CR6:</b> Treatment with cladribine tablets is unlikely to have a major impact on vaccine responses. - Some degree of immunity is preferable to no immunity in individuals who may have a reduced response to a vaccine.	8 (7.8)	91.7% N=33/36
<b>CR7:</b> The length of protection offered by COVID-19 vaccines is currently unclear. Local guidelines should be consulted regarding repeat vaccination.	9 (8.6)	100% N=36/36

**Table 2. Continued**

**Q4. When should a person with MS be vaccinated against COVID-19 if they are about to start treatment with cladribine tablets (first course in Year 1 or second course in Year 2)?<sup>a</sup>** (Level of evidence: low)

Consensus recommendation	Strength of recommendation <sup>a</sup>	Level of consensus <sup>b</sup>
<b>CR8:</b> In general, increased risk of MS disease worsening is the greater threat to long-term health in people with MS than SARS-CoV-2 infection. As a result, treatment initiation with cladribine tablets and long-term stability of MS should be prioritized over vaccination. - The risk of COVID-19 should be balanced against the benefit of treatment with cladribine tablets, taking into consideration the local infection rates versus the patient's clinical condition, including disability, age, comorbidities, and other prognostic factors.	9 (8.0)	91.7% N=33/36
<b>CR9:</b> Delay treatment or retreatment with cladribine tablets until 2-4 weeks after completing vaccination against COVID-19 <sup>a</sup> , if possible, and depending on disease activity.	8 (8.0)	91.7% N=33/36

**Q5. When should a person with MS be vaccinated against COVID-19 if they are already undergoing treatment with cladribine tablets (post course one, or post course two)?<sup>a</sup>** (Level of evidence: low)

<b>CR10:</b> If already undergoing a course of cladribine tablets, people with MS should receive COVID-19 vaccination when available and offered, regardless of lymphocyte counts or timing of the subsequent dose.	8 (7.8)	83.3% N=30/36
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**Table 3. Consensus recommendations to address clinical questions on safety of COVID-19 vaccination**

**Q6. Based on currently available data, are the COVID-19 vaccines safe for use in people with MS receiving cladribine tablets? (Level of evidence: high for the general population; low for specific population of people with MS being treated with cladribine tablets)**

<b>CR11:</b> Any approved and available COVID-19 vaccines that are not live nor live-attenuated virus are safe to use in people with MS who are being treated with cladribine tablets <sup>a,b</sup>	9 (8.3)	97.2% N=35/36
<b>CR12:</b> Upon completion of vaccination, social distancing and other protective measures should be exercised as recommended by local, regional, or national authorities.	9 (8.8)	100% N=36/36

**Q7. Will COVID-19 vaccination lead to exacerbation of MS symptoms or relapse while undergoing treatment with cladribine tablets? (Level of evidence: very low)**

<b>CR13:</b> There is currently no available evidence to indicate that vaccination against COVID-19 will lead to an MS relapse or permanent disease worsening. - Transient worsening of MS symptoms may occur as a result of COVID-19 vaccination (e.g., in the setting of fever), but this should not be confused with worsening of disease. - The overall benefits of vaccination outweigh transient worsening of MS symptoms.	9 (8.6)	100% N=36/36
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**Footnotes** <sup>a</sup>Median score on a 1-9 scale (mean score in brackets). <sup>b</sup>Percentage of votes with 7-9 on a 9-point scale. <sup>c</sup>Completing vaccination means having received all doses, depending on the approved vaccine used. <sup>d</sup>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. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on bodyweight. Following completion of the two treatment courses, no further cladribine treatment is required in Years 3 and 4 (Mavenclad SmPC). **CR**, clinical recommendation; **EF**, extended faculty; **MS**, multiple sclerosis; **Q**, question; **SC**, steering committee.

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