Post-Approval Safety of Cladribine Tablets in the Treatment of Patients With Multiple Sclerosis: 2024 Update

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OBJECTIVES

To provide an update on the post-approval safety profile of cladribine tablets in people with relapsing multiple sclerosis (RMS).

INTRODUCTION

Cladribine tablets (3.5 mg/kg over 2 years) are an established disease-modifying therapy for people with RMS.[1]

The favorable safety profile of cladribine tablets for the management of RMS has previously been described.[2]

Following completion of the two treatment courses, no further treatment with cladribine tablets is required in Years 3 and 4.[3, 4]

Since the EU approval in 2017 and US approval in 2019, an estimated 101,132 people have received cladribine tablets for the treatment of MS with 251,900 cumulative years of exposure.[5]

METHODS

- Adverse events (AEs) from post-approval sources (including spontaneous individual case safety reports, non-interventional post-marketing studies, and reports from other solicited sources) are presented through July 2024.
  - The number of individual case safety reports and the number of associated AEs are reported.
- For AEs of special interest, adjusted reporting rates per 100 patient-years are reported along with the corresponding 95% confidence interval (CI).
- Note that serious infections/lymphopenia are reported instead of severe events, as severity is generally not reported in the post-approval setting.

RESULTS

Table 1. Summary of Reports (as of July 7, 2024)

AEs of special interest	Adjusted reporting rate[a] per 100 patient-years, (95% CI)
Hypersensitivity *(2858 reports)*	1.13 (1.09, 1.18)
Serious infections *(1270 reports)*	0.50 (0.48, 0.53)
Herpes zoster *(830 reports)*	0.33 (0.31, 0.35)
Liver injury *(623 reports)*	0.25 (0.23, 0.27)
Malignancies[b] *(397 reports)*	0.16 (0.14, 0.17)
Serious lymphopenia *(259 reports)*	0.10 (0.09, 0.12)
Seizures *(160 reports)*	0.06 (0.05, 0.07)
Opportunistic infections (excluding PML[c] and tuberculosis) *(39 reports)*	0.02 (0.01, 0.02)
Tuberculosis *(35 reports)*	0.01 (0.01, 0.02)

[a]The reporting rate is adjusted for the cumulative duration of patient exposure to cladribine tablets. [b]The spectrum of malignancies resembled the distribution of cancer types seen in the general population, without any clustering of specific tumor types. [c]As of July 7, 2024, there were no confirmed cases of PML.

AE, adverse event; CI, confidence interval; PML, progressive multifocal leukoencephalopathy

Hypersensitivity

- A total of 2858 reports were noted; the majority (98%) of the 566 cases (674 AEs) in the latest reporting period (July 8, 2023–July 7, 2024) were non-serious (**Supplementary Figure 1**).

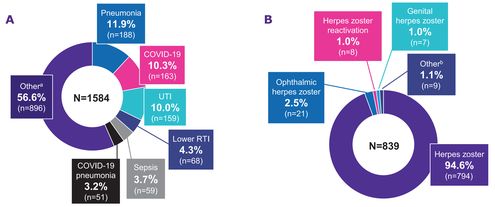
Serious infections

- A total of 1270 reports concerning 1584 serious infections were noted. The most frequently reported events are reported in **Figure 1A.**

Herpes zoster

- A total of 830 reports concerning 839 herpes zoster AEs were noted (serious events, n=61). The most frequently reported events are reported in **Figure 1B**.

Figure 1. Events of (A) Serious infections and (B) Herpes zoster



[a]Other includes: kidney infection (n=43), diverticulitis (n=39), herpes zoster and influenza (n=37, each), infection (n=27), urosepsis (n=26), and cellulitis (n=23). Other serious infections occurred <20 times within the reports and are not detailed here.

[b]Other includes: herpes zoster oticus (n=3), oral herpes zoster (n=2), herpes zoster disseminated, herpes zoster infection neurological, herpes zoster meningitis and herpes zoster meningoencephalitis (n=1, each).

n, number of events; RTI, respiratory tract infection; UTI, urinary tract infection

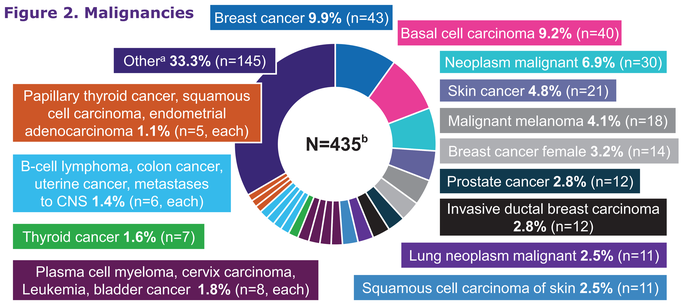
Liver injury

- A total of 623 reports concerning 837 AEs were noted; two cases (five AEs) had a fatal outcome. Of these, one event was described as liver failure likely secondary to isoniazid toxicity and unrelated to cladribine. The other four events occurred in one single patient with a history of drug-induced liver injury and other risk factors.
- Of the 228 serious AEs, the most common were increased alanine aminotransferase (n=45) and increased aspartate aminotransferase (n=35).
- Non-serious AEs (n=609) mostly pertained to liver enzyme elevations. In several cases, a medical history of episodes of liver parameter elevations with other drugs was reported.

Malignancies

- A total of 397 reports (435 AEs) were noted (**Figure 2**).
- Safety data concerning malignancies do not show a pattern of clustering.
- Malignancy occurrence was in line with that expected in the general population.[6]

Figure 2. Malignancies



[a]Other includes events with a frequency <5.

[b]Events ≥5 are displayed; events <10 are grouped. n, number of events; CNS, central nervous system

Serious lymphopenia

- A total of 259 reports (260 AEs) concerning serious lymphopenia were noted; 69 cases were associated with infections (104 AEs, of which 59 were serious).
- Serious co-reported infections occurring more than once included:
  - COVID-19 (n=5), urinary tract infection (n=4), pneumonia and urosepsis (n=3, each), COVID-19 pneumonia, influenza, ophthalmic herpes zoster, lower respiratory tract infection, and subcutaneous abscess (n=2, each).
- None of the co-reported infections were fatal.

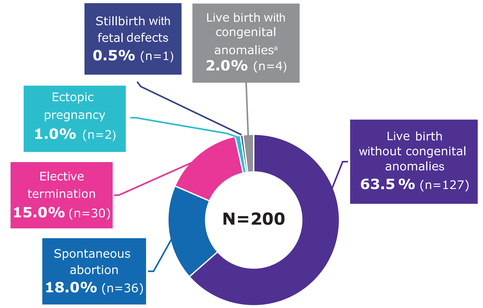
Opportunistic infections other than tuberculosis

- A total of 39 reports concerning opportunistic infections other than tuberculosis were noted; 23 were serious and included:
  - Ophthalmic herpes (n=7)
  - Infection susceptibility increased, esophageal candidiasis, ophthalmic herpes simplex (n=2, each)
  - Atypical mycobacterial infection, cytomegalovirus infection, histoplasmosis disseminated, meningitis cryptococcal, meningomyelitis herpes, nocardiosis, opportunistic infection, pneumonia cryptococcal, pneumonia fungal, and pulmonary histoplasmosis (n=1, each)
- No case of progressive multifocal leukoencephalopathy causally associated with cladribine tablets treatment was reported.

Pregnancy outcomes

- A total of 474 pregnancies were identified; 200 pregnancies have known outcomes (**Figure 3**).

Figure 3. Known pregnancy outcomes



[a]Of the four live births with congenital anomalies, one was major (atrial septal defect) and three were minor.

n, number of events

- While data are currently scant and therefore caution should be taken on the interpretation of the results of a small number of cases, there is no evidence for an increased risk of adverse pregnancy outcomes in patients receiving cladribine tablets.

CONCLUSIONS

- **Cumulative to July 7, 2024, the safety profile as observed in the real-world setting of cladribine tablets is consistent with findings from the clinical development program[7, 8] and previous safety updates.[9]**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References: 1. Giovannoni G, Mathews J. *Neurol Ther.* 2023;11:571–595. 2. Clavelou P, et al. *Neurol Ther.* 2023;12:1457–1476; [Erratum: *Neurol Ther.* 2024;13:255–256]. 3. Mavenclad European Public Assessment Report Product Information [Online]. https://www.ema.europa.eu/en/medicines/human/EPAR/mavenclad. 4. Mavenclad US Prescribing Information (2024). https://www.emdserono.com/us-en/pi/mavenclad-pi.pdf. 5. Hillert J, et al. *Clin Epidemiol.* 2024;16:717–732. 6. GLOBOCON 2022. https://gco.iarc.who.int/. 7. Cook S, et al. *Mult Scler Relat Disord.* 2019;29:157–167. 8. Leist T, et al. *Mult Scler Relat Disord.* 2020;46:102572. 9. Giovannoni G, et al. *Mult Scler.* 2022;28(3S):364.

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