Cladribine Tablets in the Treatment of Patients With Multiple Sclerosis: 2023 Post-Approval Safety Update

Gavin Giovannoni[1], Thomas Leist[2], Dominic Jack[3], Andrew Galazka[4], Nektaria Alexandri[5], Axel Nolting[5]

[1]Blizard Institute, Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK; [2]Division of Clinical Neuroimmunology, Jefferson University, Comprehensive MS Center, Philadelphia, PA, USA; [3]Merck Serono Ltd., Feltham, UK, an affiliate of Merck KGaA, Darmstadt, Germany; [4]Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany; [5]the healthcare business of Merck KGaA, Darmstadt, Germany

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CONCLUSIONS

Cumulative to July 2023, the safety profile of cladribine tablets has been consistent with findings from the clinical development program[3,4] and previous safety updates[5]

While data are currently limited, there is no evidence of an increased risk of adverse pregnancy outcomes in patients receiving cladribine tablets

INTRODUCTION

- Cladribine tablets (3.5 mg/kg cumulative dose over 2 years) are an established disease-modifying therapy for patients with relapsing multiple sclerosis (MS).[1] A recent review has indicated the favorable safety profile of cladribine tablets for the management of such patients[2]
- As of December 2023, an estimated 89,397 patients have received cladribine tablets with 203,904 patient-years of exposure since approval in 2017

OBJECTIVES

To update on the post-approval safety profile of cladribine in patients with MS

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 to July 2023

For AEs of special interest, adjusted incidences per 100 patient-years (P-Y) are reported along with the corresponding 95% confidence interval (CI); crude values are shown for hypersensitivity and seizures

Note that serious infections/lymphopenia are reported instead of severe events, as severity is generally not reported in the post-approval setting

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of patients with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults).

RESULTS

Table 1. Summary of AEs (as of July 2023)

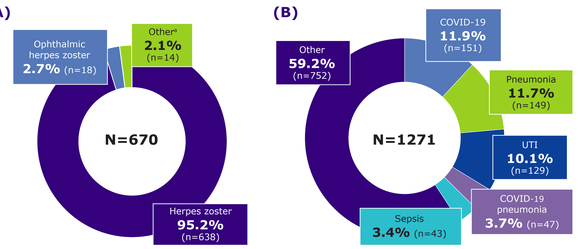
AEs of special interest	Adjusted incidence rate[a] per 100 patient-years (95% CI)
Serious lymphopenia (151 reports)	0.09 (0.08, 0.11)
Herpes zoster (665 reports)	0.41 (0.38, 0.44)
Serious infections (1028 reports)	0.63 (0.60, 0.67)
Opportunistic infections other than PML[b] and tuberculosis (22 reports)	0.01 (0.01, 0.02)
Malignancies[c] (285 reports)	0.18 (0.16, 0.20)
Liver injury (488 reports)	0.30 (0.28, 0.33)
Tuberculosis (26 reports)	0.02 (0.01, 0.02)
Hypersensitivity (2368 reports)	0.030[d]
Seizures (133 reports)	0.002[d]

[a]The cumulative patient duration of exposure to cladribine tablets. [b]No confirmed case of PML as of July 2023. [c]The spectrum of malignancies resembled the distribution of cancer types seen in the general population, without any clustering of specific tumor types. [d]Crude incidence rate
AE, adverse event; **CI**, confidence interval; **PML**, progressive multifocal leukoencephalopathy

Herpes zoster and serious infections

- A total of 665 reports concerning 670 herpes zoster AEs were noted (serious events, n=48). The most frequently reported events are reported in **Figure 1A**
- A total of 1028 reports concerning 1271 serious infections were noted. The most frequently reported events are reported in **Figure 1B**
- Of the serious infections, 21 events were fatal: COVID-19, pneumonia (n=4, each), urosepsis (n=2), COVID-19 pneumonia, endocarditis bacterial, lower respiratory tract infection, nocardiosis, pharyngitis, respiratory tract infection, sepsis, septic embolus, septic shock, urinary tract infection and infection (each reported once)*

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



[a]Other includes genital herpes zoster, herpes zoster reactivation, herpes zoster infection neurological, meningitis, meningoencephalitis, and oticus (n=1 each)
UTI, urinary tract infection

Opportunistic infections other than PML and tuberculosis

- A total of 22 reports concerning opportunistic infections other than progressive multifocal leukoencephalopathy (PML) and tuberculosis were noted; 18 were serious and included:
  - Ophthalmic herpes (n=6)
  - Infection susceptibility increased (n=2)
  - Meningomyelitis herpes, esophageal candidiasis, nocardiosis, ophthalmic herpes simplex, histoplasmosis disseminated, cryptococcal pneumonia, cytomegalovirus infection, pulmonary histoplasmosis, atypical mycobacterial pneumonia, and cryptococcal meningitis (n=1 each)

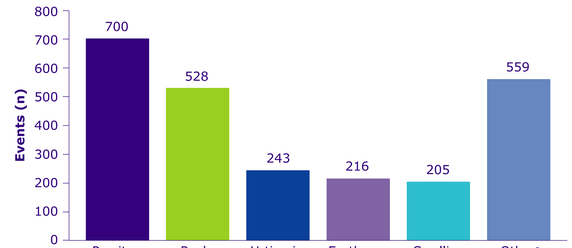
Liver injury

- A total of 488 reports concerning 670 AEs were noted; one drug-induced liver injury was fatal, but was deemed unrelated to cladribine tablets
- Of the 188 serious AEs, the most common were increased alanine aminotransferase (n=40) and increased aspartate aminotransferase (n=31). Non-serious AEs (n=482) mostly pertained to liver enzyme elevations. In several cases, a medical history of episodes of liver parameter elevations with other drugs was reported

Serious lymphopenia and hypersensitivity

- Of the 151 serious lymphopenia cases (152 events), 67 were associated with infections (40 serious)
- Serious co-reported infections occurring more than once included COVID-19 (n=5), urinary tract infection (n=4), COVID-19 pneumonia, subcutaneous abscess, and urosepsis (n=2 each); none of the co-reported infections were fatal
- A total of 2368 reports of hypersensitivity AEs were noted **(Figure 2)**

Figure 2. Hypersensitivity Events



[a]Other includes pruritic (n=228), erythematous (n=119), macular (n=112), papular (n=67), or vesicular (n=33)
Swelling includes facial (n=71), periphery (n=62), eyes (n=40), or lips (n=32)

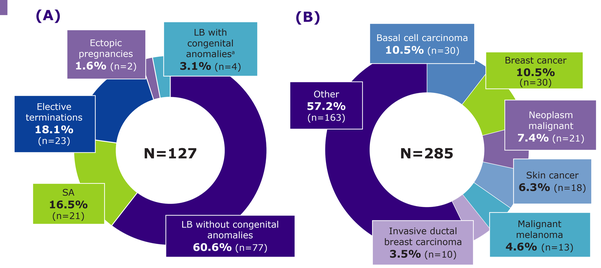
Pregnancy outcomes

- A total of 333 pregnancies were identified; 127 pregnancies have known outcomes **(Figure 3A)**

Malignancies

- A total of 285 reports (282 serious AEs) were noted **(Figure 3B)**
- Of the malignancies, the following six were fatal: lung adenocarcinoma (n=2), lung neoplasm malignant, lung cancer metastatic, lung carcinoma cell type unspecified stage IV, and metastasis (n=1 each)

Figure 3. (A) Pregnancy Outcomes, and (B) Malignancies



[a]Of the four pregnancies resulting in live births with congenital anomalies, one was major (atrial septal defect), and three were minor
LB, live birth; **SA**, spontaneous abortion

*Current as of June 18, 2024

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1. Giovannoni G & Mathews J. *Neurol Ther*. 2023;11(2):571–595; 2. Clavelou P, et al. *Neurol Ther*. 2023;12(5):1457–1476; 3. Cook S, et al. *Mult Scler Relat Disord*. 2019;29:157–167; 4. Leist T, et al. *Mult Scler Relat Disord*. 2020;46:102572; 5. Giovannoni G, et al. *Mult Scler*. 2022;28(3S):364.

Disclosures: GG has received speaker honoraria and consulting fees from AbbVie, Actelion (Janssen/J&J), Atara Bio, Almirall, Bayer, Biogen, Celgene (Bristol Myers Squibb), FivePrime, GlaxoSmithKline, GW Pharma, Ironwood, Merck & Co., the healthcare business of Merck KGaA, Darmstadt, Germany, Moderna, Novartis, Pfizer Inc., Protein Discovery Laboratories, Roche, Sanofi, Teva, UCB, Vertex Pharmaceuticals, and Viracta; and has received research support unrelated to this study from Biogen, Ironwood, Merck & Co., the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, and Takeda. **TL** has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, and Teva. **DJ** is an employee of Merck Serono Ltd., Feltham, UK, an affiliate of Merck KGaA, Darmstadt, Germany. **AG** is a former employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany, and is currently a consultant to the healthcare business of Merck KGaA, Darmstadt, Germany. **NA** and **AN** are employees of the healthcare business of Merck KGaA, Darmstadt, Germany.

Medical writing assistance was provided by Meghan Bradley and Claire Mwape of inScience Communications, Springer Healthcare Ltd, UK, and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany.

Presented at ACTRIMS 2024 Forum | February 29–March 2 | West Palm Beach, FL, USA

Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)