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Updated Post-Approval Safety of Cladribine Tablets in the Treatment of Multiple Sclerosis, With Particular Reference to Liver Safety

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- Several integrated analyses have reported on the safety of cladribine tablets (3.5 mg/kg cumulative dose over 2 years) during the clinical development program for relapsing MS^{1,2}
- As of July 2022, an estimated 56,300 patients with MS have received cladribine tablets with 95,664 patient-years of exposure since approval in 2017
- Providing continual presentation of relevant new safety data concerning cladribine tablets, as they become available, is important for the medical community





To update on the post-approval safety profile of cladribine tablets in patients with relapsing MS, including liver safety





- Serious and non-serious AEs from post-approval sources (including spontaneous individual case safety reports, non-interventional and interventional post-marketing studies, and reports from other solicited sources) are presented to July 2022, with a focus on AEs of special interest, hypersensitivity AEs, and liver injury
- For AEs of special interest, adjusted incidences per 100 patient-years are reported along with the CI; crude values are shown for hypersensitivity AEs and liver injury

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





Summary of AEs of Special Interest (as of July 07, 2022)

- No new risks were identified during the period July 08, 2021 until July 07, 2022
- Adjusted incidences per 100 patient-years for AEs of special interest:
 - **Herpes zoster** (514 reports), 0.54 (95% CI: 0.49–0.59)
 - **Serious infections** (754 reports), 0.79 (95% CI: 0.73–0.85)
 - **Serious lymphopenia** (112 reports), 0.12 (95% CI: 0.10–0.14)
 - **Opportunistic infections** (15 reports), 0.02 (95% CI: 0.01–0.03)
 - **Progressive multifocal leukoencephalopathy**, 0
 - **Tuberculosis** (23 reports), 0.02 (95% CI: 0.02–0.04)
 - **Malignancies** (187 reports),^a 0.20 (95% CI: 0.17–0.23)
 - **Congenital anomalies** (3 reports),^b 0.003 (95% CI: 0.001–0.010)

^aThe spectrum of malignancies resembled the distribution of cancer types seen in the general population, without any clustering of specific tumor types

^bIn one case of maternal exposure during pregnancy reported by a health authority, an elective termination was performed due to an unspecified congenital anomaly of the fetus after cladribine exposure in the first trimester. In a second spontaneous case of maternal exposure (2 months) before pregnancy, a live birth with congenital anomaly (microduplication of chromosome 16p11.2) was reported. The third case concerned a low birth weight infant with hereditary sickle cell trait born after pregnancy during cladribine exposure





Herpes Zoster

A total of 514 reports of AEs concerning herpes zoster were noted, including:

- Herpes zoster (494)
- Ophthalmic herpes zoster (14)
- Genital herpes zoster (4)
- Herpes zoster reactivation (4)
- Herpes zoster meningitis (1)
- Herpes zoster meningoencephalitis (1)

Serious Infections

A total of 754 reports of AEs concerning serious infections were noted, including:

- Urinary tract infection (117)
- COVID-19 (103)
- Pneumonia (96)
- COVID-19 pneumonia (42)
- Lower respiratory tract infection (37)
- Herpes zoster (36)
- Sepsis (34)
- Influenza (24)
- Kidney infection (24)
- Nasopharyngitis (24)
- Infection (23)
- Cellulitis (17)
- Diverticulitis (17)
- Urosepsis (17)
- Respiratory tract infection (14)
- Bronchitis (12)
- Cystitis (12)
- Ophthalmic herpes zoster (12)
- Upper respiratory tract infection (12)
- Oral herpes (11)
- Sinusitis (10)

Serious Lymphopenia

- Among the 112 reports of serious lymphopenia, 43 were associated with infections.
- The outcome of such events was reported as recovered or recovered with sequelae (13), recovering (10), not recovered (8), and unknown/not reported (12).





Opportunistic Infections Other Than PML and Tuberculosis

Fifteen reports of AEs concerning opportunistic infections (other than PML and tuberculosis) were noted, including:

- Ophthalmic herpes (5)
- Oral herpes (3)
- Infection susceptibility increased (2)
- Gastrointestinal fungal infection, histoplasmosis disseminated, meningomyelitis herpes, nocardiosis, ophthalmic herpes simplex, opportunistic infection, cryptococcal pneumonia, and toxoplasmosis (1 each)

Hypersensitivity

A total of 1810 reports of hypersensitivity AEs were noted, including:

- Rash (410)
- Pruritic (183), erythematous (103), macular (99), papular (51), or vesicular (26) rash
- Pruritus (536)
- Urticaria (167)
- Erythema (162)
- Swelling of the face (49)



Liver Injury

- During post-marketing experience, uncommon events of liver injury, including serious cases leading to discontinuation of treatment, were reported in temporal association with cladribine tablets

Cases of Liver Injury, by Severity

| CIOMS DILI Grade | Post-approval reports | | Clinical trials | Total |
|--------------------|-----------------------|-------------|-----------------|-------|
| | Serious | Non-serious | | |
| Grade 1 (mild) | 27 | 14 | 2 | 43 |
| Grade 2 (moderate) | 14 | 0 | 0 | 14 |
| Grade 3 (severe) | 2 | 0 | 0 | 2 |
| Grade 4 (fatal) | 1 | 0 | 0 | 1 |
| Total | 44 | 14 | 2 | 60 |

The Grade 4 case (fatal) concerned a patient with a history of alcoholic liver disease, tuberculosis, and a persisting pulmonary tuberculosis lesion. The patient was placed on isoniazid and cladribine was started thereafter. Serum transaminases were grossly elevated at clinical manifestation of liver injury. The reporter associated the causality of fatal liver injury to isoniazid toxicity

- Isolated cases of transient serum transaminase elevations up to 40-fold the upper limit of normal and/or symptomatic hepatitis with transient elevation of bilirubin and jaundice have been observed
- Time to onset varied, with most cases occurring within 8 weeks after the first treatment course

Further guidance on monitoring of liver function is provided as part of US prescribing information¹

Patients should have their serum aminotransferase, alkaline phosphatase, and total bilirubin levels assessed prior to the first and second treatment courses of cladribine

If a patient develops clinical signs of liver injury during treatment, liver enzyme and bilirubin monitoring should be obtained and cladribine treatment should be promptly interrupted or discontinued, as appropriate



- Cumulative to July 2022, the safety profile of cladribine tablets is consistent with findings from the clinical development program
- Liver toxicity was identified as an important but uncommon risk of cladribine tablets

