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

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CONCLUSIONS

Cumulative to July 2022, the safety profile of cladribine tablets is consistent with findings from the clinical development programme

Liver toxicity was identified as an important but uncommon risk of cladribine tablets

INTRODUCTION

- Several integrated analyses have reported on the safety of cladribine tablets (3.5 mg/kg cumulative dose over 2 years) during the clinical development programme for relapsing multiple sclerosis (MS)[1,2]
- As of July 2022, an estimated 56,300 patients 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

OBJECTIVE

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

METHODS

- Serious and non-serious adverse events (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 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 corresponding 95% confidence interval (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.

RESULTS

Summary of AEs (as of 7 July 2022)

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

[a]The spectrum of malignancies resembled the distribution of cancer types seen in the general population, without any clustering of specific tumour types.

[b]In 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 foetus 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)

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)

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)

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 (**Table 1**)
- 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

Table 1. 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[a]
Total	44	14	2	60

CIOMS, Council for International Organisations of Medical Sciences; **DILI**, drug-induced liver injury

[a]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.

Further guidance on monitoring of liver function is now provided as part of updated EU prescribing information[3]

Before initiating cladribine tablets, a comprehensive patient history regarding previous episodes of liver injury with other drugs or underlying liver disorders should be taken. Patients should have their serum aminotransferase, alkaline phosphatase, and total bilirubin levels assessed prior to initiation of therapy in Year 1 and Year 2. During treatment, liver enzyme and bilirubin monitoring should be obtained based on clinical signs and symptoms.

REFERENCES
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