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Post-approval Safety of Cladribine Tablets With Particular Reference to COVID-19 Outcomes: An Update

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CONCLUSIONS

Regarding COVID-19, patients treated with cladribine tablets are generally not at greater risk of serious disease and/or a severe outcome compared with the general population and other patients with MS who acquired COVID-19

The post-approval safety profile of cladribine tablets is consistent with previously published safety findings from the clinical development program

INTRODUCTION

- The safety profile of cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) from the clinical development program for relapsing MS is well characterized[1]
- Additional real-life safety data have accrued since the approval of cladribine tablets in >80 countries worldwide

OBJECTIVE

To update on the post-approval safety profile of cladribine tablets in patients with relapsing MS, with particular reference to COVID-19

METHODS

- We previously reported on outcomes for cladribine tablets-treated patients with relapsing MS and confirmed or suspected COVID-19 (as of 29 June 2020 and 15 January 2021, respectively)[2,3]
- An update on these findings is provided, as of 15 July 2021, based on cases reported to the Merck Global Patient Safety Database
  - Cases meeting the criteria of hospitalized, medically significant (as specified by the case reporter), or fatal were designated as serious
  - Outcomes were classified as per usual pharmacovigilance practice
  - Time to onset of COVID-19 from the most recent annual treatment course with cladribine tablets was also evaluated
- A summary of post-approval, real-world AEs is also provided

RESULTS

Summary of COVID-19 Cases (as of 15 July 2021)

- The safety database included 503 reported cases of COVID-19 in cladribine tablets-treated patients
- Six additional patients had symptoms compatible with COVID-19 but were not evaluated further since they were subsequently reported to have negative PCR tests

	All patients (n=503)	Serious COVID-19 (n=68)
Median age, years (range)	41 (17–73)	48 (24–73)
Aged ≥60 years, n (%)	27 (5.4)	8 (11.8)
Not reported, n (%)	89 (17.7)	3 (4.4)
Sex, n (%)		
Male	101 (20.1)	16 (23.5)
Female	339 (67.4)	50 (73.5)
Not reported	63 (12.5)	2 (2.9)
Confirmed COVID-19,[a] n (%)	316 (62.8)	51 (75.0)

[a]According to PCR test or serology.
Cases meeting the criteria of hospitalized, medically significant (as specified by the case reporter), or fatal were designated as serious.

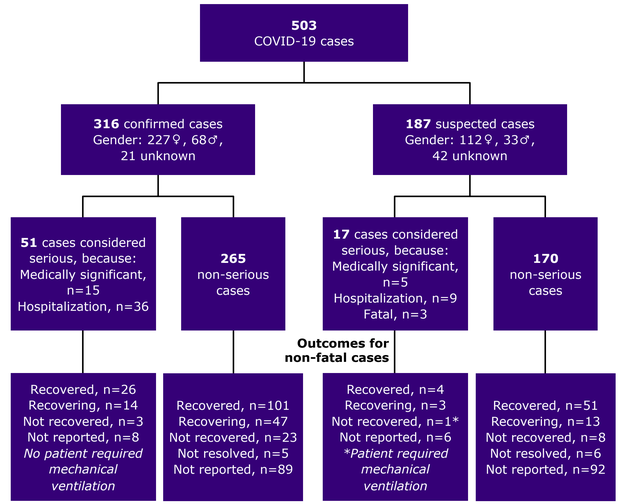
Summary of Adverse Events (as of 7 July 2021)

- To date, 35,668 patients who received cladribine tablets post-approval (49,783.5 patient-years of exposure)
- Adjusted incidences per 100 patient-years for AEs of special interest:
  - Severe lymphopenia (72 cases), 0.14 (95% CI: 0.11–0.18)
  - Herpes zoster (362 cases), 0.73 (95% CI: 0.66–0.81)
  - Tuberculosis (16 cases), 0.03 (95% CI: 0.02–0.05)
  - Severe infections (479 cases), 0.96 (95% CI: 0.88–1.05)
  - Progressive multifocal leukoencephalopathy, 0
  - Opportunistic infections (9 cases), 0.02 (95% CI: 0.01–0.03)
  - Malignancies (108 cases), 0.22 (95% CI: 0.18–0.26)
  - Congenital anomalies (2 cases),[a] 0.004 (95% CI: 0.001–0.016)

[a]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 fetus after cladribine exposure in the third trimester. In the second spontaneous case of maternal exposure (2 months) before pregnancy, a live birth with congenital anomaly (microduplication of chromosome 16p11.2) was reported.

Summary of COVID-19 Outcomes (as of 15 July 2021)

- Of 503 evaluable patients, 259 (51.5%) were recovered/recovering at the time of reporting
- Among 68 serious cases, 47 (69.1%) were recovered/recovering at the time of reporting
  - One patient (suspected COVID-19) required mechanical ventilation
  - There were 3 fatalities (0.6% of all patients; all had suspected COVID-19)
    - One patient died in late 2020 having experienced pneumonia and renal failure
    - One patient died in early 2021 (no further details reported)
    - One patient died in early 2021 having experienced stroke complicated by pneumonia
- Median (range) time to onset of COVID-19 from most recent treatment course:
  - All patients, 169 (0–684) days (n=314)
  - Serious cases, 184 (4–643) days (n=52)



Cases meeting the criteria of hospitalized, medically significant (as specified by the case reporter), or fatal were designated as serious. For simplicity of presentation, the outcome 'not reported' also includes those with missing or pending outcomes.

Abbreviations: **AE**, adverse event; **CI**, confidence interval; **MS**, multiple sclerosis; **PCR**, polymerase chain reaction.| **References**: 1. Cook S, et al. *Mult Scler Relat Disord*. 2019;29:157–167. 2. Jack D, et al. *Mult Scler Relat Disord*. 2020;46:102469. 3. Jack D, et al. *Mult Scler Relat Disord*. 2021;51:102929.

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