# Updated Safety of Cladribine Tablets in the Treatment of Patients with Multiple Sclerosis: Integrated Safety Analysis and Post-approval Data

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## CONCLUSIONS

**The updated safety profile from this analysis, containing final data from the PREMIERE registry cumulative to October 2018, was generally consistent with that from previously published analyses (cumulative to February 2015 and cumulative to May 2017).[4,5]**

**No new major safety findings were identified in this finalized integrated analysis.**

**No new safety signals were identified in the real-world post-approval data, cumulative to January 2020.**

## INTRODUCTION

- The safety of treatment with cladribine tablets was assessed in the clinical trial program,[1-3] including the CLARITY[1] and CLARITY Extension[2] studies in patients with relapsing multiple sclerosis (RMS).
- Integrated safety data (cumulative to February 2015 and cumulative to May 2017) for cladribine tablets have previously been published.[4,5]
  - Integrated analysis of pooled clinical safety data is an established method facilitating the comprehensive characterization of the safety profile of a therapy.
- There have been additional safety data obtained from use in clinical practice since the approval of cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as cladribine tablets 3.5 mg/kg) in many countries around the world.
  - In addition to clinical data, we present the sum total of serious adverse events (AEs) from the reporting of post-approval data.
- This analysis represents the final analysis of data from the clinical development of cladribine tablets and moving forward there will be only post-approval updates.

## OBJECTIVE

1. **Provide an update to the previously reported cumulative serious treatment-emergent AEs (TEAE) profile of cladribine tablets 3.5 mg/kg from the clinical trial program following integration of final data from the PREMIERE Registry, completed in October 2018.**
2. **To report post-approval safety data from worldwide sources, cumulative to January 2020.**

## METHODS

### Post-approval Data

- The sum total of serious AEs, as well as individual numbers of serious and non-serious AEs from post-approval sources are reported.
  - Post-approval sources included spontaneous individual case safety reports (i.e. health care professionals, consumers, competent authorities [worldwide], and scientific literature), non-interventional post-marketing studies, and reports from other solicited sources.

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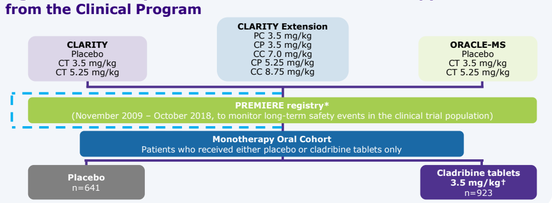
## METHODS (continued)

### Monotherapy Oral Cohort Data

- The Monotherapy Oral cohort comprised patients from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry (**Figure 1**):
  - 923 patients received cladribine tablets 3.5 mg/kg.
  - 641 patients received placebo.
- Adjusted adverse event incidences per 100 patient-years (Adj-AE per 100PY) were calculated, using a data cut-off of October 2018 (end of the PREMIERE registry).

*Patients with prior enrollment into selected clinical trials with cladribine tablets were eligible to enter PREMIERE once participation in the clinical trial had ended. †The Monotherapy Oral cohort also contained a cladribine tablets (CT) 5.25 mg/kg treatment group; data not shown. All safety analyses were performed using the "as treated principle". For the Monotherapy Oral Cohort, if patients received only placebo or were in the observational follow-up period without having switched to CT (i.e. in CLARITY Extension [Ext]), then their data became part of the placebo group. Patients who switched treatment from placebo to CT in subsequent studies/periods had their time on placebo censored at the time of the switch. Patients who switched treatment from placebo to CT 3.5 mg/kg had their time on CT 3.5 mg/kg initiated at the time of switching. Patients who were treated with CT 3.5 mg/kg in CLARITY and were then re-exposed to CT 3.5 mg/kg in a subsequent study/period (i.e. in CLARITY Ext) had their time on CT 3.5 mg/kg censored at the time of re-exposure. CP 3.5 mg/kg: CT 3.5 mg/kg in CLARITY followed by placebo in CLARITY Ext; CP 5.25 mg/kg: CT 5.25 mg/kg in CLARITY followed by placebo in CLARITY Ext; CC 7 mg/kg: CT 3.5 mg/kg in CLARITY followed by CT 3.5 mg/kg in CLARITY Ext; CC 8.75 mg/kg: CT 5.25 mg/kg in CLARITY followed by CT 3.5 mg/kg in CLARITY Ext; PC 3.5 mg/kg: placebo in CLARITY followed by CT 3.5 mg/kg in CLARITY Ext.

**Figure 1. Summary of Data Included in the Monotherapy Oral Cohort from the Clinical Program**




## RESULTS

**Table 1. Characteristics of Patients Included in the Monotherapy Oral Cohort from the Clinical Program**

| Patient characteristic | Placebo (n=641) | Cladribine tablets 3.5 mg/kg (n=923) |
|---|---|---|
| Patient-years* | 2422 | 3937 |
| Time on study, years*, mean (SD) | 3.78 (2.66) | 4.27 (2.53) |
| Time on study, ≥96 weeks [~2 years], n (%) | 493 (76.9) | 784 (84.9) |
| Time on study, ≥192 weeks [~4 years], n (%) | 204 (31.8) | 431 (46.7) |
| Time on study, ≥432 weeks [~9 years], n (%) | 18 (2.8) | 26 (2.8) |
| Age, years†; mean (SD)<br>Median<br>Min; max | 37.15 (9.83)<br>36.53<br>18.1; 64.2 | 37.84 (10.48)<br>37.62<br>18.2; 66.1 |
| Age ≤40 years, n (%) | 396 (61.8) | 540 (58.5) |
| Age >40 years, n (%) | 245 (38.2) | 383 (41.5) |
| Female, n (%) | 424 (66.1) | 612 (66.3) |
| Prior treatment with DMD, n (%) | 131 (20.4) | 184 (19.9) |

*Cumulative to October 2018; †As reported at first dosing date. **DMD**, disease-modifying drug; **SD**, standard deviation.

### Monotherapy Oral Cohort Data

- Patient characteristics were generally balanced among groups (**Table 1**).
- The reported number of serious TEAEs was higher in the cladribine tablets 3.5 mg/kg group versus the placebo group (**Table 2; Additional Content Supplementary Table 1**).
- In the cladribine tablets 3.5 mg/kg group, the Adj-AE for serious lymphopenia was 0.10 per 100PY (**Table 2**).
  - Lymphopenia is an expected pharmacological effect of cladribine tablets due to its mechanism of action.
- In the cladribine tablets 3.5 mg/kg group, serious infections occurred more frequently than in the placebo group (**Table 2**).
  - The incidence of herpes zoster was higher in the cladribine-treated group than in the placebo group, but serious respiratory infections occurred at a similar frequency.
- Malignant tumor incidence rates were similar to those in the previously published analysis (**see additional safety data within Additional Content**).[4,5]

### Post-approval Data

- A total of 2570 AEs were reported in the first 14,813 patients who received cladribine tablets post-approval.
- In total, 303 (12%) of the 2570 AEs were classified as serious during the reporting period, none of which represented a new safety signal.
- Overall, the pattern of serious and non-serious AEs observed was consistent with the clinical safety profile for cladribine tablets.
- AEs of special interest with cladribine tablets 3.5 mg/kg are presented as crude incidences in **Table 3**.

**Table 2. Serious* TEAEs of Special Interest in the Monotherapy Oral Cohort from the Clinical Program**

| | Placebo (n=641) | | | Cladribine tablets 3.5 mg/kg (n=923) | | |
|---|---|---|---|---|---|---|
| | n | Total PY | Adj-AE per 100PY | n | Total PY | Adj-AE per 100PY |
| At least 1 serious TEAE | 68 | 2226.2 | 3.05 | 133 | 3498.1 | 3.80 |
| Lymphopenia | 0 | 2421.5 | 0 | 4 | 3925.4 | 0.10 |
| Herpes zoster | 0 | 2421.5 | 0 | 2 | 3929.7 | 0.05 |
| Pneumonia | 3 | 2415.2 | 0.12 | 6 | 3907.4 | 0.15 |
| Pulmonary tuberculosis | 0 | 2421.5 | 0 | 1 | 3933.6 | 0.03 |
| Tuberculosis | 0 | 2421.5 | 0 | 1 | 3936.7 | 0.03 |
| Urinary tract infection | 1 | 2419.9 | 0.04 | 4 | 3923.4 | 0.10 |
| Malignancies | 3 | 2414.8 | 0.12 | 10 | 3918.9 | 0.26 |
| Rash generalized | 0 | 2421.5 | 0 | 1 | 3936.6 | 0.03 |

*Serious was defined as resultant in death, life-threatening, required inpatient hospitalization, congenital anomaly or birth defect, or was otherwise considered as medically important. **Adj-AE per 100PY**, adjusted adverse events incidences per 100 patient-years; **PY**, patient-years; **TEAE**, treatment-emergent adverse events.

**Table 3. Adverse Events of Special Interest (Serious and Non-serious) in the Monotherapy Oral Cohort from the Clinical Program and the Analysis of Post-approval Data (Until 7 January 2020)**

| | Monotherapy Oral Cohort cladribine tablets 3.5 mg/kg (n=923) | | Post-approval Cohort cladribine tablets 3.5 mg/kg (n=14,813) | |
|---|---|---|---|---|
| | n | AE rate (crude incidence) | n | AE rate (crude incidence) |
| Severe lymphopenia | 24 | 0.03 | 27‡ | 0.002 |
| Herpes zoster | 28 | 0.03 | 117 | 0.008 |
| Tuberculosis | 2† | 0.002 | 6 | 0.0004 |
| Severe infections | 29 | 0.03 | 138‡ | 0.009 |
| PML | 0 | 0 | 0 | 0 |
| Opportunistic infections* | 10 | 0.01 | 19 | 0.001 |
| Malignancies | 10 | 0.01 | 22 | 0.0015 |
| Teratogenicity | 0** | 0 | 0§ | 0 |

The Monotherapy Oral Cohort comprises patients from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry; AE rates are based on the numbers of patients with at least one AE. Post-approval Cohort comprises the first 14,813 patients treated with cladribine tablets using post-approval sources from 22 August 2017 to 7 January 2020 (N.B. patients in this cohort were not systematically followed); AE rates are based on the overall number of AEs.
*Majority of the opportunistic infections were mucocutaneous and cutaneous fungal infections, which resolved on standard treatments. Opportunistic infections that could be life-threatening were not observed.
**No cases of teratogenicity in pregnancies occurred during cladribine treatment or within 6 months after the last dose.
†Both cases of tuberculosis in the Monotherapy Oral Cohort were serious (one coded as tuberculosis, one coded as pulmonary tuberculosis).
‡In the Post-approval Cohort, all serious events were counted towards severe lymphopenia and severe infections.
§In one case of maternal exposure during pregnancy reported by a Health Authority (#E2B, 90073559), an elective termination was performed due to a congenital anomaly of the fetus (not further specified). Exposure to cladribine tablets occurred in the first trimester. The patient was on concomitant medication with terbutaline and ferrous sulfate which could adversely impact fetal development.
**AE**, adverse event; **n**, number of events; **PML**, progressive multifocal leukoencephalopathy.

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