Updated Safety of Cladribine Tablets in the Treatment of Multiple Sclerosis: Safety Analysis of Post-approval Data

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INTRODUCTION

- The safety of treatment with cladribine tablets was assessed in the clinical trial program.1-4 including the CLARITY and CLARITY Extension studies, 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.5-8
- There are no lymphopenia safety data obtained from use in clinical practice since the approval of cladribine tablets 11 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 (SAE) from the reporting of post-approval data.

OBJECTIVES

- To 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
- To report post-approval safety data from worldwide sources.

METHODS

Monotherapy Oral Cohort: Data from the Clinical Program

- 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 incidence per 100 patient-years (Adj-AE per 100PY) were calculated, using a data cut-off of October 2018 and the PREMIERE registry.

Monotherapy Oral Cohort Data: From the Clinical Program

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

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

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Cladribine tablets 3.5 mg/kg (N = 923)</th>
<th>Placebo (N = 641)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/year</td>
<td>141 (33.8)</td>
<td>100 (23.6)</td>
</tr>
<tr>
<td>Time in study, weeks</td>
<td>215.7 (SD 28.8)</td>
<td>223.9 (SD 29.8)</td>
</tr>
<tr>
<td>Age, year (&lt;40)</td>
<td>37.15 (9.83)</td>
<td>37.15 (9.83)</td>
</tr>
<tr>
<td>Age, year (&gt;40)</td>
<td>36.53 (9.83)</td>
<td>36.53 (9.83)</td>
</tr>
<tr>
<td>Time on study, years*</td>
<td>2.03 (SD 0.47)</td>
<td>2.03 (SD 0.47)</td>
</tr>
<tr>
<td>Total PY</td>
<td>3936.7 (SD 528.1)</td>
<td>3934.4 (SD 528.2)</td>
</tr>
</tbody>
</table>

*Serious was defined as resultant in death, life-threatening, required inpatient hospitalisation, congenital anomaly or birth defect, or was otherwise considered as medically important;

RESULTS

Monotherapy Oral Cohort: Patient Characteristics

- Patient characteristics were generally balanced among groups (Table 1).

Monotherapy Oral Cohort: Lymphopenia

- In the clinical trial program, 3.5 mg/kg group: 0.05 Adj-AE per 100PY; the probability of occurrence is higher during cumulative dose over 2 years; referred to as cladribine tablets 3.5 mg/kg in many countries around the world.

Monotherapy Oral Cohort: Infections

- There were no cases of progressive multifocal leukoencephalopathy with cladribine tablets 3.5 mg/kg.
- There were no cases of herpes zoster with cladribine tablets 3.5 mg/kg. In the placebo group, there were no serious herpes zoster events.

Monotherapy Oral Cohort: Malignant Lymphoma

- There were no cases of lymphoma with cladribine tablets 3.5 mg/kg. In the placebo group, there were no serious lymphoma events.

Monotherapy Oral Cohort: Other

- There were no new safety signals identified in the real-world post-approval data from the first 8419 patients to receive cladribine tablets 3.5 mg/kg.

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

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Cladribine tablets 3.5 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (100PY)</td>
<td>Adj-AE per 100PY</td>
<td>Adj-AE/100PY</td>
</tr>
<tr>
<td>All serious AEs</td>
<td>47 (9.3)</td>
<td>30 (3.7)</td>
</tr>
<tr>
<td>Hematopoietic system disorders</td>
<td>0.90</td>
<td>0.36</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Opportunistic infections*</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Malignant tumours</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Severe lymphopenia</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Severe infections and infestations</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Serious was defined as resultant in death, life-threatening, required inpatient hospitalisation, congenital anomaly or birth defect, or was otherwise considered as medically important;

CONCLUSION

- No new major safety findings were identified in this finalised integrated safety dataset from the clinical program involving 923 patients who received cladribine tablets 3.5 mg/kg.

- The updated safety profile from this analysis, continuing 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).

- Similarly, no new safety signals were identified in the real-world post-approval data from the first 8419 patients to receive cladribine tablets.

REFERENCES


DISCLOSURES

This study was sponsored by EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany, and EMD Serono, Inc., France, a business of Merck KGaA, Darmstadt, Germany, and EMD Serono, Inc., Canada, a business of Merck KGaA, Darmstadt, Germany. The authors would like to thank patients and their families, investigators, co-investigators, and the study teams at each of the participating centres and at Merck KGaA, Darmstadt, Germany. Medical writing assistance was provided by Wenchi Movih and John P. Jones of bioclinics Communications, Springer Healthcare Ltd, Chester, United Kingdom, and was funded by Merck KGaA Darmstadt, Germany (ROW). The authors would like to thank patients and their families, investigators, co-investigators, and the study teams at each of the participating centres and at Merck KGaA, Darmstadt, Germany.

ACKNOWLEDGMENTS

The Medical Economic Institute for Registry Authorities (MERICA) used to cost the adverse event coding. System Organ Class was applied by adjudication. Methodology is review of Paediatric Form A, Pneumocystis, and Trial Adjudication Form by physicians blinded to treatment from which the data were derived. Study design was performed by EMD Serono, Inc., under a contract with Merck KGaA Darmstadt, Germany.

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