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

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Short title to be displayed on app: Updated Safety Analysis of Cladribine Tablets

Background: Integrated analysis of pooled clinical safety data allows comprehensive characterisation of the safety profile of cladribine tablets (CT) 10mg (3.5mg/kg cumulative dose over 2 years [CT3.5]) in patients with relapsing multiple sclerosis (RMS). This analysis aimed to update the previously reported serious treatment emergent adverse event (TEAE) profile of CT3.5 following integration of final data from the PREMIERE registry, and report post-approval safety data from worldwide sources.

Methods: The monotherapy oral cohort (CT3.5, N=923, patient-years [PY]=3936.69; placebo [PBO], N=641, PY=2421.47) was derived from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry. Adjusted incidences per 100PY were calculated for adverse events, cumulative to the end of PREMIERE (October 2018). Serious and non-serious AEs from post-approval sources are also summarised.

Results: Patient characteristics were balanced between treatment groups (mean age [37.8 years, CT3.5; 37.2 years, PBO], proportion of females [66.3%, CT3.5; 66.1%, PBO] and proportion of patients with prior disease modifying drug experience [19.9%, CT3.5; 20.4%, PBO]). Incidences per 100PY for ≥1 serious TEAE were 3.80 (CT3.5), and 3.05 (PBO). Incidences per 100PY for serious lymphopenia (preferred term [PT]) was 0.10 (CT3.5), 0 (PBO). For serious infections and infestations (system organ class), incidences per 100PY were 0.60 (CT3.5), 0.42 (PBO); for serious herpes zoster (PT): 0.05 (CT3.5), 0 (PBO). Incidences per 100PY for malignant tumours were 0.26 (CT 3.5), 0.12 (PBO). Post-approval sources reported 1622 AEs in the Periodic Benefit-Risk Evaluation Report, of which 275 were serious; none represented a new safety signal.

Conclusions: No new major safety findings were identified in this finalised integrated dataset which includes final data from PREMIERE. This profile is consistent with the previously published integrated safety analysis profile. No new safety signals were identified in the real world post-approval data of cladribine tablets.

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SS and **DD**: employees of EMD Serono Research & Development Institute Inc., a business of Merck KGaA, Darmstadt, Germany.

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