Title: Updated safety analysis of Cladribine Tablets (CT) in the treatment of patients with multiple sclerosis (MS)

Short Title: Updated safety analysis of Cladribine Tablets

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Introduction: Integrated analysis of pooled long-term safety data allowed comprehensive characterisation of the CT safety profile in patients with relapsing MS (RMS). Previous characterisation of a monotherapy oral cohort treated with CT 3.5 mg/kg (CT3.5) included cumulative safety data to Feb 2015, >3 years beyond last clinical study completion.

Objective: Two-year update of the serious treatment emergent adverse event (TEAE) profile from the CT3.5 integrated safety analysis.

Methods: The monotherapy oral cohort was derived from CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry. 923 patients received CT3.5; 641 patients received placebo. Adjusted AE incidences per 100 patient-years (Adj-AE per 100PY) were calculated. Data cut-offs were cumulative to Feb-2015 (previously presented, “Period-1”) and cumulative to May-2017 (updated, “Period-2”). Serious adverse drug reactions (ADR; implied causality) from post-marketing sources are summarised.

Results: Demographics at respective study enrolment, including age (36.5 years, CT3.5), proportion of females (66.3%, CT3.5) and prior disease modifying drug experience, were balanced among treatment groups. Respective rates of Adj-AE per 100PY were (presented as CT3.5, placebo): ≥1 serious TEAE: 3.88, 3.24 (Period-2) and 4.00, 3.57 (Period-1); serious lymphopenia (preferred term
[PT]) 0.11, 0 (Period-2) and 0.12, 0 (Period-1); serious infection and infestations (system organ class
[SOC]): 0.63, 0.44 (Period-2) and 0.69, 0.50 (Period-1); for serious herpes zoster (PT): 0.05, 0 (Period-
2) and 0.06, 0 (Period-1); serious neoplasms, benign, malignant and unspecified (SOC) 0.65, 0.35
(Period-2) and 0.74, 0.50 (Period-1). Regarding post-marketing data, 11 serious ADRs were reported;
none are new safety findings for CT3.5.

**Conclusions:** This integrated analysis confirms the serious TEAE profile associated with CT3.5
treatment of patients with early and active RMS. The updated profile (Period-2) was generally
consistent with that from 2-years prior (Period-1). No new major safety findings were identified in
the updated dataset, where patients were followed for ≤10-years.

The CLARITY study: NCT00213135; The CLARITY Extension study: NCT00641537; The ORACLE-MS
study: NCT00725985; The PREMIERE registry: NCT01013350

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