

**Full title:** Infections and grade 3 or 4 lymphopenia in patients taking cladribine tablets 3.5 mg/kg: data from an integrated safety analysis

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**Background:** Cladribine tablets given in short courses over 2 years has demonstrated efficacy in patients with relapsing multiple sclerosis. The most common adverse event (AE) was lymphopenia, reflecting the mechanism of action of cladribine. An integrated safety analysis showed that the overall infection incidence was unchanged in patients receiving cladribine tablets 3.5 mg/kg vs placebo, except for slightly increased risk of herpes zoster (HZV).

**Objective:** This *post-hoc* analysis examined infectious AEs occurring concurrently with Grade 3 or 4 lymphopenia (with G3/4) in patients treated with cladribine tablets 3.5 mg/kg.

**Methods:** A cladribine tablets 3.5 mg/kg monotherapy oral cohort (n=923) was derived from CLARITY, CLARITY Extension, ORACLE-MS and the PREMIERE registry. The AE profile for cladribine tablets 3.5 mg/kg with G3/4 was analysed. Adjusted AE incidences per 100 patient years (Adj-AE/100PY) were calculated.

**Results:** Adj-AE/100PY for any infections/infestations with G3/4 was 57.53 vs 24.50 outside these periods (without G3/4). Types of infectious AEs with G3/4 were similar to without G3/4. More than half of cases occurring with G3/4 were easily-treatable infections of the upper respiratory tract (Adj-AE/100PY: nasopharyngitis, 13.48 vs 5.24 without G3/4; upper respiratory tract infection, 9.67 vs 3.41 without G3/4; pharyngitis; 4.51 vs 0.73 without G3/4). HZV was reported in 4 patients with G3/4 (Adj AE/100PY 4.50 vs 0.73 without G3/4); cases were dermatomal and mild to moderate in severity. Single occurrences were reported for most infectious AEs. Opportunistic infections were single occurrences of 'urinary tract infection fungal' and 'fungal infection' and neither was severe or serious. No opportunistic infections were difficult to treat.

**Conclusions:** Severe lymphopenia resulted in an increased frequency of infections but did not influence the type of infectious AEs in patients treated with cladribine tablets 3.5 mg/kg. The profile of HZV was uncomplicated, consistent with the findings of previous safety analyses.

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