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ADIS DRUG EVALUATION

Cladribine Tablets: A Review in Relapsing MS

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Abstract

Cladribine is a deoxyadenosine analogue prodrug that preferentially depletes lymphocytes, key cells underlying multiple sclerosis (MS) pathogenesis. Cladribine tablets (Mavenclad®) represent the first short-course oral disease-modifying drug (DMD) for use in MS. The tablets, administered in two short courses 1 year apart, are indicated for the treatment of adults with highly active relapsing MS on the basis of data from pivotal clinical trials, including the phase 3 study CLARITY and its extension. A cumulative cladribine tablets dose of 3.5 mg/kg administered in this fashion in CLARITY reduced clinical relapse, disability progression and MRI-assessed disease activity and also improved some aspects of health-related quality of life (HR-QOL) versus placebo over 96 weeks in adults with relapsing-remitting MS (RRMS). Moreover, in the 96-week extension (plus 24 weeks' supplemental follow-up), no additional clinical benefit was gained from continuing versus discontinuing cladribine tablets after the first two annual courses of therapy, although MRI activity was more notable in a subset of cladribine tablet recipients who discontinued the drug. In post hoc analyses of CLARITY and/or a phase 2b trial, benefits of cladribine tablets were seen in patients with high disease activity (HDA) relapsing MS that were sometimes greater than in patients without HDA. Cladribine tablets have an acceptable tolerability profile and do not appear to be associated with an increased risk of overall infection or with an increased risk of malignancy (vs. matched reference populations). Active comparisons and longer-term follow-up would be beneficial, although current data indicate that for adults with highly active relapsing MS, cladribine tablets are an effective treatment option with the convenience of low-burden, short-course, oral administration.

Cladribine tablets: clinical considerations in relapsing MS

Convenient short-course oral administration regimen
Reduce clinical relapse, disability progression and MRI-assessed disease activity and improve some aspects of HR-QOL in adults with RRMS
Provide clinical and MRI-assessed benefit in patients with high disease activity relapsing MS
Benefits continue well beyond the dosing period
Acceptable tolerability; lymphopenia is the most common issue

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1 Introduction

Multiple sclerosis (MS) is a complex, neurological disease typified by inflammation and demyelination [1, 2]. Exactly what causes MS to develop is not known, although is likely to involve a combination of genetic, environmental and immunological factors, with aberrant targeting of the CNS by the immune system likely central in the pathogenesis [2]. T (and possibly) B cells become abnormally sensitized to CNS components, causing inflammation that damages myelin, myelin-producing cells and nerve fibres, with the cytokines of these lymphocytes also playing a key role in this process [2]. The damaged areas (or 'lesions') impair the conduction of nerve impulses, resulting in neurological symptoms such as paraesthesia, muscle weakness, dizziness, blurred/double vision and cognitive impairment, which can be disabling [2, 3].

MS can take various forms, of which the most common is relapsing-remitting MS (RRMS) [i.e. symptomatic periods followed by complete/partial recovery], although this often degenerates to secondary progressive MS (SPMS) [i.e. overall worsening of neurological function with time, sometimes with superimposed relapses] [2]. Indeed, MS can have a highly active course in some patients, as indicated by various clinical (e.g. frequent/severe relapses, incomplete relapse recovery, early physical/cognitive impairment accumulation) and imaging (e.g. heavy lesion burden, increasing lesion frequency despite MS therapy, early brain atrophy) features [4], although there is currently no consensus as to what constitutes highly active MS.

In the absence of curative therapies, the aim of treating MS is to reduce the risk of relapse and disability progression [1]. To this end, several disease-modifying drugs (DMDs) are available for use, one of the latest of which is cladribine (2-chlorodeoxyadenosine), a deoxyadenosine analogue prodrug that preferentially depletes lymphocytes. Cladribine tablets (Mavenclad®) are approved for the treatment of highly active relapsing MS in the EU [5], with this article providing an overview of data relevant to their use in this setting.

2 Pharmacodynamic Properties of Cladribine

Once uptaken by cells, cladribine has a prolonged intracellular residence time (due to its resistance to the purine-degrading enzyme, adenosine deaminase [5]) and is phosphorylated to its active triphosphate moiety (CdATP) by intracellular deoxycytidine kinase (DCK) [5, 6]. This process occurs especially well in lymphocytes, due to their high DCK levels and low levels of 5′-nucleotidase (5′-NTase; an enzyme that dephosphorylates and inactivates CdATP) [5, 7], making lymphocytes particularly prone to CdATP accumulation [8]. As it accumulates, CdATP inhibits DNA synthesis in dividing cells [6, 9] and leads to DNA strand breaks and reductions in intracellular NAD and ATP levels in quiescent cells [10]. CdATP is lethal to both dividing and resting lymphocytes [11], with cell death occurring via mechanisms such as apoptosis and/or autophagy [8, 12, 13]; in human leukaemia cells, CdATP induced apoptosis via caspase-dependent and –independent pathways involving mitochondria [14].

Cladribine tablets reduce peripheral lymphocyte levels in patients with MS, which may interrupt the central immune cascade of the disease [5]. For instance, in adults with RRMS who received cladribine tablets at the recommended cumulative dose of 3.5 mg/kg (hereafter referred to as cladribine tablets 3.5 mg/kg) over 96 weeks in the phase 3 trial CLARITY (Sect. 5), lymphocyte counts declined rapidly from baseline (median 1900 cells/μL) after daily administration of the drug for 4–5 days in weeks 1 and 5 (course 1) and weeks 48 and 52 (course 2) [15]. Nadir occurred at weeks 9 and 60, with the median changes from baseline at these timepoints being −45.8 and −55.9% [15]. After each nadir, lymphocyte counts gradually increased but remained lower than at baseline, with the median change from baseline being −35.6% at week 48 and −43.5% at week 96 [15]. Among the lymphocytes, B cells ($CD19^+$) were reduced more markedly than T cells ($CD3^+$, $CD4^+$ or $CD8^+$) or natural killer cells ($CD16^+/CD56^+$), although the B-cell reductions were shorter lived [16]. Among the T cells, $CD8^+$ T cells were reduced to a lesser extent by cladribine than $CD4^+$ T cells and also recovered more quickly [16], thus reducing the $CD4^+$:$CD8^+$ ratio [5]. Such differences in cladribine sensitivity may be due to the differing DCK: 5′-NTase ratios of the lymphocytes [5, 7]. Longer-term pooled follow-up data from patients who received a 3.5 mg/kg cumulative dose of cladribine tablets over 96 weeks (in this trial or its extension) then no further active treatment (including in a safety registry; PREMIERE) indicate that 75% of cladribine tablet recipients may have normal lymphocyte levels at week 144 [17].

Cells of the innate immune system and those produced by the bone marrow have lower DCK: 5′-NTase ratios than lymphocytes and are thus impacted less by cladribine [5]. Indeed, although neutrophil, haemoglobin, red blood cell, platelet and haematocrit levels have declined with cladribine tablets in clinical trials, they often stayed within the limits of normal [5] (e.g. 69–89% of cladribine tablet vs. 76–95% of placebo recipients maintained normal neutrophil, haemoglobin and platelet levels over 96 weeks in CLARITY [15]).

In addition to lymphocyte depletion, preclinical data suggest that cladribine may induce caspase-independent apoptosis of dendritic cells (antigen-presenting cells capable of re-priming myelin-specific T cells) [18] and may [19] or may not [20] impact microglia (CNS macrophages). Other properties displayed by the drug in vitro include immunomodulation [e.g. inhibition of T-cell activation/cytokine secretion [21], induction of a more anti-inflammatory cytokine response by peripheral blood mononuclear cells (PBMCs) [22] and reduction of inflammatory cytokine/chemokine secretion by dendritic cells [23]] and reduction of PBMC migration in a blood-brain-barrier model [24]. Cladribine also reduced serum levels of some soluble adhesion molecules (sICAM-1 and sE-Selectin, but not sVCAM-1) involved in regulating entry of inflammatory cells into the brain in MS patients [25] and had direct neuroprotective effects in a murine model of MS by interfering with the effects of interleukin-1β at synapses [20].

However, given the concentrations of cladribine in some preclinical studies were much higher than those achieved in patients, the exact mechanism(s) by which cladribine tablets exert benefit in patients with MS is not yet clear [26].

3 Pharmacokinetic Properties of Cladribine

Absorption of cladribine after oral administration is rapid, with a median time to peak plasma concentration of 0.5 h in the fasted state and 1.5 h when taken with a high-fat meal [5, 27]; the drug can be taken without regard to food [5]. Cladribine is 20% plasma protein bound [5], and has a large mean volume of distribution (480–490 L), indicating extensive distribution to tissues and intracellular uptake [5, 27]. Within target cells, cladribine undergoes phosphorylation to form various metabolites, including the active triphosphate form, CdATP, which has an intracellular half-life of 10 h. The phosphorylated metabolites and/or parent drug accumulate substantially within lymphocytes, with in vitro data suggesting that accumulation may be evident as early as 1 h after being exposed to cladribine (intracellular vs. extracellular accumulation ratio: ≈30–40) [5, 28]. Potential for cladribine to cross the blood-brain-barrier was evident in cancer patients in a small study (cerebrospinal fluid/plasma concentration ratio: ≈0.25) [5].

No major metabolites have been identified in the plasma, with the unchanged parent drug being the main circulating component after oral administration [29]. Around 60% of a single dose of cladribine is excreted unchanged [29], with elimination occurring via renal and non-renal routes [5]. Its renal clearance (median 22.2 L/h) exceeds the rate of glomerular filtration and thus likely involves active tubular secretion [28]. Non-renal clearance of cladribine (median 23.4 L/h) occurs through its extensive intracellular distribution and its active moiety being trapped within target cells and subsequently eliminated [5, 28]. Hepatic metabolism of cladribine is minimal, accounting for < 10% of the total clearance of the drug [29]. Although cladribine has an estimated terminal half-life of ≈ 1 day, its half-life accounts for little of its exposure and the drug does not accumulate when administered once daily [5].

Mild renal impairment (creatinine clearance 60–89 mL/min) may increase exposure to cladribine, although no adjustment in dosage is considered necessary [5]. However, cladribine tablets are contraindicated in patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min), as its efficacy/safety in these patients has not been established [5]. Although hepatic metabolism contributes minimally to cladribine elimination, the drug is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh score > 6) due to a lack of data. Cautious use of cladribine tablets is advised in elderly patients, because of the increased likelihood of hepatic/renal impairment, comorbidities and other treatments [5].

4 Drug Interaction Profile of Cladribine

During the few days that cladribine tablets are taken (Sect. 7), their administration should be separated (by ≥ 3 h) from that of other oral drugs, to avoid any potential increases in bioavailability that may result from such drugs forming complexes with hydroxypropylbetadex (a solubility-enhancing agent contained within cladribine tablets) [5].

Cladribine tablets are contraindicated for use in patients receiving immunosuppressive or myelosuppressive agents, as there may be additive effects on the immune system; however, systemic corticosteroids may be used short term during cladribine therapy [5]. There is also potential for additive haematological adverse reactions to occur if cladribine tablets are administered before, or in conjunction with, other drugs that impact the blood (e.g. carbamazepine); haematological parameters should therefore be carefully monitored with such combinations. The risk of lymphopenia with cladribine tablets (Sect. 6.1) is increased if they are used in combination with interferon-β, whereas their safety/efficacy in combination with other DMDs has not been determined; concomitant use of cladribine tablets and other DMDs is not recommended [5].

Cladribine is a substrate of various transporter proteins, including BCRP, ENT1 and CNT3, which facilitate its passage across cell membranes [5]. Its oral bioavailability and systemic exposure may therefore increase upon inhibition of gastrointestinal BCRP (e.g. by eltrombopag, a known BCRP inhibitor), whereas the net impact that potent ENT1 and CNT3 inhibitors (e.g. cilostazol, dilazep, nifedipine, nimodipine, reserpine, sulindac) may have on cladribine exposure

is hard to predict. These interactions are of unknown clinical relevance, although drugs that potently inhibit BCRP, ENT1 or CNT3 should be avoided during the 4- to 5-day periods that cladribine tablets are administered; if this is not possible, various alternative approaches are recommended [5]. Exposure to cladribine may decrease if coadministered with potent inducers of BCRP or P-gp (e.g. corticosteroids, rifampicin, St. John's wort), although this has not been evaluated formally. It is not known if cladribine tablets impact hormonal contraceptive efficacy; thus, barrier contraception is advised during treatment with cladribine tablets, and for ≥ 4 weeks after the last dose in each of the annual treatment courses [5].

5 Therapeutic Efficacy of Cladribine

This section reviews the efficacy of cladribine tablets in adults with RRMS, as evaluated in a 96-week, double-blind, placebo-controlled, phase 3 trial, known as CLARITY [15], and its extension [30]. Data from various subgroup analyses of CLARITY and a phase 2b trial (ONWARD) are also discussed; some data are from abstracts/posters [31–33].

Patients eligible for CLARITY had active RRMS (i.e. at least one relapse in last 12 months) and a score of ≤ 5.5 on the Expanded Disability Status Scale (EDSS) [scored 0–10, with higher scores reflecting more disability] [15]. Patients who had relapsed within 28 days of the study were excluded, as were those who had already failed at least two DMDs or received prior immunosuppressive therapy. Eligible patients were randomized to receive cladribine tablets or placebo in two 48-week treatment courses, with discussion here focusing on the recommended cumulative cladribine tablet dose of 3.5 mg/kg (i.e. cladribine tablets 3.5 mg/kg; see Table 1 for details). After week 24, patients with ≥ 1 relapse or a sustained increase in EDSS score could receive subcutaneous interferon-β1a as rescue therapy; intravenous corticosteroids could be used to treat relapses at the physician's discretion. Overall, at baseline, patients had a mean age of 38–39 years, a mean disease duration of 7.9–9.3 years ($p = 0.005$ across treatment groups) and a mean EDSS of 2.8–3.0; 26–33% had received prior DMD therapy and 66–69% were female [15].

After completing CLARITY, eligible patients could enter a 96-week double-blind extension, which was followed by 24 weeks of supplemental follow-up. Patients originally randomized to cladribine tablets 3.5 mg/kg were re-randomized to cladribine tablets 3.5 mg/kg (i.e. cladribine → cladribine) or placebo (i.e. cladribine → placebo) and those originally randomized to placebo were switched to cladribine tablets 3.5 mg/kg (i.e. placebo → cladribine) (Table 1) [30]. As

Table 1 Efficacy of cladribine tablets in adults with RRMS in the 96-week phase 3 trial CLARITY and its 96-week extension plus 24 weeks of supplemental follow-up

Endpoints	CLARITY [15, 34]		CLARITY extension (includes supplemental follow-up)[a] [30, 31, 37]		
	Cladribine ($n = 433$)	Placebo ($n = 437$)	Cladribine → cladribine ($n = 186$)	Cladribine → placebo ($n = 98$)	Placebo → cladribine ($n = 244$)
Clinical outcomes					
Annualized relapse rate	0.14**[b]	0.33[b]	0.10	0.15	0.10$^{\delta\delta}$
Pts (%) without relapse	79.7**	60.9	81.2	75.6	79.6$^{\delta\delta}$
Pts (%) without 3-mo sustained cDP	85.7*	79.4	77.4	72.4	75.8
MRI-assessed lesions (values are means)					
Gd+ T1 lesions	0.12**	0.91	0.03$^{\dagger\delta}$	0.28$^{\delta}$	0.07$^{\delta}$
Active T2 lesions	0.38**	1.43	0.88	1.42	1.07
Combined unique lesions[c]	0.43**	1.72			
T1 hypointense lesions	6.7**	6.9	NR[d]	NR[d]	NR[d]

Cladribine (as one or two 10 mg tablets) or placebo was administered daily for 4–5 days in weeks 1 and 5 (course 1; cumulative dose 1.75 mg/kg) and weeks 48 and 52 (course 2; cumulative dose 1.75 mg/kg) of both CLARITY and its extension; the overall cumulative cladribine dose in each of these 96-week studies was 3.5 mg/kg. During supplemental follow-up, use of disease-modifying drugs (other than cladribine) was permitted if necessary

cDP confirmed disability progression, *Gd+* gadolinium enhancing, *mo* month, *NR* not reported, *pts* patients, → switched to

*$p < 0.05$, **$p < 0.001$ vs. PL; $^{\dagger}p < 0.001$ vs. cladribine → placebo; $^{\delta}p < 0.001$, $^{\delta\delta}p < 0.0001$ vs. at end of CLARITY

[a]Statistical comparisons included cladribine → placebo vs. cladribine → cladribine or placebo → cladribine

[b]Primary endpoint

[c]Defined as new Gd+ T1 lesions and/or new non-enhancing or enlarging T2 lesions (without double counting)

[d]Between-group differences were reported as being not significant; endpoint was not prespecified

this was not a pre-planned extension, the bridging interval between the last CLARITY visit and entry into the extension varied, although the range was similar within each of the respective treatment groups (0.4–115, 0.1–116 and 0.3–118 weeks). Few patients received DMD therapy within the bridging interval (two in the cladribine → placebo group and four in the placebo → cladribine group) [30].

5.1 Relapse and Disability Progression

Cladribine tablets 3.5 mg/kg reduced the rate of clinical relapse in adults with RRMS, with the primary endpoint of annualized relapse rate (ARR) being significantly reduced by 57.6% with the drug versus placebo over 96 weeks in CLARITY (Table 1) [15]. Other endpoints supported these findings, with cladribine tablets being significantly more favourable than placebo in terms of the time to first relapse (13.4 vs. 4.6 months; $p < 0.001$) and the proportion of patients who remained relapse free (Table 1), required rescue therapy (2.5 vs. 6.2%; $p = 0.01$), or were free from 3-month confirmed disability progression (Table 1) at 96 weeks [15].

Clinical outcomes were durable with cladribine tablets in the 96-week extension of this trial plus the 24 weeks of supplemental follow-up (Table 1). For instance, after 120 weeks, the cladribine → placebo group did not significantly differ from the cladribine → cladribine group in terms of ARR or the proportion of patients who remained relapse free (Table 1) [30]. This suggests that further clinical benefit may not be gained from continuing cladribine tablets after the first two courses of treatment and that rebound of clinical disease activity is unlikely after discontinuation of the drug, at least in the 120-week timeframe assessed here. As expected, the placebo → cladribine group was the only extension group to have a significantly lower ARR [30] and a significantly higher relapse-free rate [31] at the end of the extension plus supplemental follow-up than at the end of CLARITY (consistent with the overall trial findings) (Table 1), although an analysis of CLARITY and the extension together found this group had the shortest time to first relapse, highlighting the potential drawback of delaying treatment [30].

5.2 MRI-Assessed Disease Activity

Cladribine tablets 3.5 mg/kg reduced MRI-assessed disease activity, as measured by lesion frequency, in adults with RRMS in CLARITY. Compared with placebo, the drug significantly reduced the frequency of gadolinium-enhancing (Gd+) T1 lesions, active T2 lesions, combined unique lesions and T1 hypointense lesions by 86, 73, 74 and 3%, respectively, over the 96-week study (Table 1) [15, 34]. There were also significantly ($p < 0.001$) more cladribine tablet than placebo recipients free from lesions (Gd+ T1, active T2 or combined unique) at study end (60–87 vs. 26–48%) [34].

Cladribine tablets significantly reduced T2 lesion volume (by 24%) relative to placebo in CLARITY (mean change from baseline at 96 weeks was −2.2 vs. −1.8 mL; $p < 0.001$) [34], a noteworthy finding given the correlation observed between increased T2 lesion volume and loss of brain tissue/integrity [35]. In support of these findings, an exploratory analysis of this trial found significantly less brain atrophy in cladribine tablet ($n = 336$) than placebo ($n = 338$) recipients, as measured by the annualized mean percentage brain volume change (PBVC) between months 6 and 24 (−0.56 vs. −0.70%; $p = 0.01$) [36]. This outcome correlated with the cumulative likelihood of disability progression, with lower PBVCs being associated with the greatest probability of remaining free from disability progression after 96 weeks [36].

Patients who had received cladribine tablets in CLARITY sustained a low Gd + T1 lesion frequency in the 96-week extension (plus 24 weeks of supplemental follow-up), regardless of whether they had continued to receive cladribine tablets (i.e. cladribine → cladribine) or were switched to placebo (i.e. cladribine → placebo) (Table 1) [37]. This benefit was greater in the cladribine → cladribine than the cladribine → placebo group [with the former group displaying a significantly ($p < 0.001$) lower frequency of new Gd+ lesions vs. CLARITY and the latter group a significantly ($p < 0.001$) greater frequency [31]]; however, no significant difference was evident between the two groups in the frequency of active T2 lesions or T1 hypointense lesions (Table 1) [37]. Lesion-free rates at the end of the extension were consistent with these findings [37]. In the cladribine → placebo group, Gd+ T1 lesion activity appeared to be more prevalent in patients with the longest bridging interval (> 43 weeks) between CLARITY and its extension (post hoc analysis) [37]; note, patients with such prolonged intervals finished the CLARITY extension 6.5 years after starting CLARITY versus ≈ 4.5 years for those with intervals of ≤ 4 weeks [31]. The MRI findings in the third extension group (placebo → cladribine) supported the overall efficacy of cladribine tablets observed in CLARITY (Table 1) [37].

5.3 Other Outcomes

When the effect of cladribine tablets 3.5 mg/kg on overall disease activity was evaluated post hoc in CLARITY, significantly ($p < 0.0001$) more cladribine tablet than placebo recipients were free from disease activity (defined as no relapse, 3-month sustained disability progression or new Gd+ T1 or active T2 lesions) over 24, 48 and 96 weeks (e.g. 44 vs. 16% over 96 weeks, at which point 402 and 379 patients were evaluable) [38].

Some aspects of health-related quality of life (HR-QOL) improved with cladribine tablets over 96 weeks in CLARITY [39]. For instance, cladribine tablets were associated with significant ($p < 0.05$) improvements versus placebo in the EuroQol five-dimension questionnaire (EQ-5D) index score at several timepoints, including 24, 72 and 96 weeks. Mean changes from baseline in each of the five EQ-5D dimensions (mobility, self-care, activity, pain and anxiety) favoured cladribine tablets over placebo at the latter timepoint, although only self-care reached statistical significance ($p = 0.008$). No significant differences in HR-QOL were evident between cladribine tablets and placebo when measured using the EQ-5D visual analogue scale (perhaps due to its sensitivity limitations) or the Multiple Sclerosis Quality of Life-54 questionnaire (possibly due to the low number of respondents; ≤ 65 in each group) [39].

5.4 In Highly Active Disease and Other Subgroups

Patients with highly active MS benefit from cladribine tablets, according to post hoc analyses of CLARITY in which high disease activity (HDA) was defined either as: (1) high relapse activity (HRA) [i.e. ≥ 2 relapses in the last year [38, 40], regardless of treatment status [40]] plus ≥ 1 Gd+ T1 lesion or ≥ 9 T2 lesions [38] or any number of such lesions [40] or (2) HRA plus disease activity on treatment (DAT) [i.e. ≥ 1 relapse in the last year plus ≥ 1 Gd+ T1 or ≥ 9 T2 lesions] [40]. For instance, in the most recent analysis [40], cladribine tablets provided significant benefit over placebo in the HDA subgroups for every outcome evaluated, which included the time to 6-month confirmed disability progression, ARR, cumulative number of lesions (new Gd+ T1, active T2 or cumulative unique lesions), and 'no evidence of disease activity' score. For the time to 6-month confirmed disability progression and 'no evidence of disease activity' score, the relative benefit of cladribine tablets versus placebo was significantly greater ($p < 0.05$ for interaction) in the HRA ($n = 261$) and/or HRA + DAT ($n = 289$) group than in patients without these characteristics ($n = 1190$); however, no significant interactions were evident for any of the other outcomes.

In two further analyses [32, 33] (post hoc where specified [32]), cladribine tablet regimens provided benefit in patients with SPMS with relapses, another population considered to have HDA. In one of the analyses, which used data from ONWARD (a phase 2b study that compared cladribine tablets with placebo, as an add-on to interferon-β therapy in patients with SPMS plus relapses or with RRMS), cladribine tablets significantly reduced the ARR by 89% in patients with SPMS ($n = 26$) and by 50% in patients with RRMS ($n = 171$) [32]. The other analysis, which used pooled data from CLARITY and ONWARD, found significant (nominal $p < 0.0001$) ARR reductions with cladribine tablets versus placebo of 53% in patients with an EDSS ≥ 3.5 (an SPMS proxy) [$n = 414$] and 60% in those with an EDSS ≤ 3.0 ($n = 653$), with no significant subgroup-by-treatment interaction [33].

According to additional post hoc data from CLARITY, the benefits of cladribine tablets versus placebo in reducing relapse [41] and lesion burden [34] and achieving freedom from disease activity [38] in adults with RRMS were evident regardless of patient/disease characteristics, such as age [38, 41], gender [41], MS duration [38, 41], disease [34, 38, 41] or disability [38, 41] burden, and history of relapse [34, 38, 41] or DMD use [38, 41].

6 Tolerability of Cladribine

The cladribine tablets 3.5 mg/kg regimen has an acceptable tolerability profile in adults with RMS. At 96 weeks in CLARITY, adverse events (AEs) had occurred in a large majority of cladribine tablet ($n = 430$) and placebo ($n = 435$) recipients (80.7 vs. 73.3%), although these were not often serious (8.4 vs. 6.4%) and caused few patients to discontinue treatment (3.5 vs. 2.1%) [15]. The most frequent AEs (incidence ≥ 3%) with at least a twofold greater incidence with cladribine tablets than with placebo included lymphopenia (21.6 vs. 1.8%), leukopenia (5.6 vs. 0.7%), alopecia (3.5 vs. 1.1%), viral upper respiratory tract infection (see Sect. 6.2) and decreased lymphocyte count (3.0 vs. 0%) [42]. Lymphopenia and uterine leiomyoma were the most common serious AEs that had an incidence with cladribine tablets at least twice that of placebo (0.7 vs. 0% incidence for each), with lymphopenia also being the AE that most often led to treatment discontinuation (0.5 vs. 0%) [42]. Few patients (0.5%) in either group died during or after withdrawal from the trial, with none of the deaths considered likely to be study drug related [15]. The tolerability profile of cladribine tablets in the CLARITY extension [30] was generally consistent with that observed in CLARITY.

Cladribine tablets are contraindicated for use during pregnancy (as there is potential for congenital malformations, given the drug interferes with DNA synthesis), and breastfeeding is contraindicated during treatment with cladribine tablets and for 1 week after the last dose (as serious adverse reactions may occur in the infants) [5]. Pregnancy should be prevented during treatment with cladribine tablets and for ≥ 6 months after the last dose; if pregnancy does occur during treatment, cladribine tablets should be discontinued [5].

6.1 Lymphopenia

As expected from its mechanism of action (Sect. 2), lymphopenia was one of the most clinically relevant adverse

reactions to occur with cladribine tablets 3.5 mg/kg over 2 years in patients with MS in clinical trials [5]. In CLARITY, grade 3 or 4 lymphopenia occurred in 25.6% of cladribine tablet and 0.5% of placebo recipients over 96 weeks (11.4 vs. 0.2% of recipients in weeks 0–48; 22.1 vs. 0.2% in weeks 48–96); however, grade 4 lymphopenia was rare (0.7 vs. 0% of placebo recipients) and generally occurred in the cladribine tablet recipients who had grade 3 lymphopenia when the drug was re-administered [42]. Among the cladribine tablet recipients who experienced grade 3 or 4 lymphopenia in this trial ($n = 107$ and 3), grade 4 lymphopenia did not persist and grade 3 lymphopenia persistence was uncommon (10 recipients) [42]; indeed, within 9 months, most cladribine tablet recipients are expected to have normal lymphocyte counts or grade 1 lymphopenia [5]. In the CLARITY extension, the incidence of grade 3 or 4 lymphopenia was low in the cladribine→placebo group (5.1%) and all cases recovered (mean time to recovery 41 days) [30].

To reduce the likelihood of severe lymphopenia occurring with cladribine tablets, lymphocyte counts should be checked before, during and after administration of the drug, and the recommended criteria for starting and continuing therapy should be adhered to. These criteria include: (1) having a normal lymphocyte count before starting cladribine tablets in year 1; (2) having ≥ 800 lymphocytes/μL before starting cladribine tablets in year 2; and (3) delaying the year 2 treatment course for ≤ 6 months if lymphocyte recovery is necessary and ceasing treatment with cladribine tablets if recovery takes ≥ 6 months [5]. Cladribine tablets are contraindicated for use in patients who are immunocompromised [5].

6.2 Infections

The incidence of infections/infestations was 24.93 per 100 patient-years (PY) with cladribine tablets ($n = 923$) versus 27.05 per 100 PY with placebo ($n = 641$) in patients with RRMS in an integrated analysis of monotherapy data from the cladribine tablets clinical development programme [which included CLARITY, its extension, a phase 3 study in early MS (ORACLE-MS) and the PREMIERE safety registry] (abstract/poster data) [43]. In CLARITY, there was an inverse correlation ($p = 0.003$) between infection development and the lowest absolute lymphocyte counts in cladribine tablet recipients [15]. Nevertheless, infections/infestations occurred with an incidence of ≈ 45% with cladribine tablets as well as with placebo in this 96-week trial (47.7% vs. 42.5%) and were generally mild or moderate in severity and rarely serious (2.3 vs. 1.6%) [15, 42]; those that occurred most frequently with cladribine tablets and with an incidence at least twofold greater than with placebo included viral upper respiratory tract infection (3.0 vs. 1.1%), vaginal infection (1.9 vs. 0.2%) and herpes zoster (1.9 vs. 0%) [42].

Herpes zoster was considered to be one of the most clinically relevant adverse reactions with cladribine tablets 3.5 mg/kg over 2 years in MS trials [5]. In the integrated analysis [43], herpes zoster occurred with an incidence of 0.83 per 100 PY with cladribine tablets (vs. 0.20 per 100 PY with placebo) and was more common during periods with, than without, grade 3 or 4 lymphopenia (2.16 vs. 0.75 per 100 PY). However, a clear association between herpes zoster and lymphopenia severity was not evident in a serial lymphocyte count analysis in CLARITY [42]. Among the few cladribine tablet recipients who developed herpes zoster in this trial (1.9%), all cases were dermatomal and localized and one was serious [42]. The incidence of herpes zoster remained low (≤ 2.0%) in all treatment groups of the CLARITY extension [30].

Cladribine tablets are contraindicated for use in patients with HIV infection or active chronic infection (tuberculosis or hepatitis), and also carry various other infection-related warnings and precautions [5]. These include screening for latent infections (before initiating the drug); delaying use of cladribine tablets when necessary (e.g. until infections have been adequately treated/fully controlled and patients without prior varicella zoster virus exposure have been fully vaccinated); and monitoring for herpes zoster and other infections (if < 500 lymphocytes/μl) and administering anti-herpes prophylaxis when necessary (i.e. if < 200 lymphocytes/μl). When to administer cladribine tablets in relation to live/attenuated vaccines (and vice versa) also requires consideration. There are no reports of progressive multifocal leukoencephalopathy (PML) with cladribine tablets in the MS clinical study database ($n = 1976$), although it has occurred with a different cladribine formulation/regimen in another therapeutic setting; thus, a baseline MRI scan should be performed for MS patients before starting to receive cladribine tablets [5].

6.3 Malignancies

Over 96 weeks in CLARITY, neoplasms (malignant, benign or unspecified) occurred in 1.4% of cladribine tablet recipients (vs. no placebo recipients), half of which were malignancies [15]. In the three cladribine tablet recipients with a malignancy (ovarian carcinoma, melanoma or pancreatic carcinoma), it was diagnosed within 12–17 months after the first treatment course [42]. The malignancy risk with cladribine tablets in this trial was no higher than that of a matched reference population when compared post hoc [standardized incidence ratio (SIR) was 0.99; 95% CI 0.25–2.70] [42].

Moreover, the CLARITY extension found no clear evidence that malignancies/unspecified tumours increased in incidence over time, including in the cladribine→placebo group (2 of 98 patients; 2.0%) [30].

Longer term, the integrated analysis (which had up to 8 years' follow-up) reported a malignancy incidence of 0.29 per 100 PY with cladribine tablets versus 0.15 per 100 PY with placebo, with the between-group difference in risk not being significant on the basis of the 95% confidence interval (−0.166 to 0.414) [abstract data] [44]. Malignancies of common origin were not clustered and lymphoproliferative, haematological and virus-induced malignancies were not observed; there was also no increase in malignancy risk over time [44]. Comparison of the data from this analysis with that of a matched reference population found no significant increase in malignancy risk with cladribine tablets, with the SIR being 0.97 (95% CI 0.44–1.85) with the drug and 0.48 (95% CI 0.14–1.53) with placebo [44]. Moreover, in a meta-analysis of phase 3 trials in patients with MS, the risk of malignancy with cladribine tablets (any dose) in CLARITY was shown not to differ significantly from that of other DMDs (0.34 vs. 0.67%), whereas the malignancy incidence in the placebo group of CLARITY was significantly lower than that in the placebo groups of all other trials (0 vs. 1.19%; $p = 0.0159$) [45]. However, cladribine tablets are contraindicated in patients with active malignancies and requires a risk/benefit evaluation before being used in patients with prior malignancy [5].

7 Dosage and Administration of Cladribine

For adults with highly active relapsing MS, the recommended cumulative dose of cladribine tablets is 3.5 mg/kg over 2 years, with a treatment course of 1.75 mg/kg being administered each year [5]. A treatment course comprises two treatment periods (one at the start of the first month of the year and the other starting in the second month), each of 4 or 5 days' duration, with a single 10 or 20 mg dose of cladribine tablets (depending on bodyweight) being taken each day. Once the two treatment courses have been completed, no further treatment with cladribine tablets is needed in the 2 years that follow (i.e. years 3 and 4); re-treatment with the drug after year 4 has not been evaluated [5].

Cladribine 10 mg tablets should be taken orally (without chewing), with or without food [5]. Before initiating cladribine tablets, the mechanism and duration of effect of any prior immunomodulatory or immunosuppressive therapies requires consideration and a baseline MRI to be taken [5]. Local prescribing information should be consulted for further details, including the lymphocyte criteria required to initiate/continue treatment with cladribine tablets, distribution of the yearly dose between the two treatment periods of each year, tablet distribution within each treatment period, drug interactions, use in special patient populations, contraindications and other warnings and precautions.

8 Place of Cladribine in the Management of MS

Therapeutic options for relapsing forms of MS have expanded greatly since the introduction of first-generation DMDs (i.e. interferon-β and glatiramer acetate), thus increasing the opportunity for more personalized therapy [1, 46, 47]. All currently available DMDs are thought to act by reducing immune-mediated inflammation in the CNS [46], although vary with regard to the mechanism(s) by which they achieve this, as well as their risks, monitoring needs and routes of administration [1]. This can make treatment individualization complex (particularly as comprehensive consensus guidance has lagged behind agent availability [1]); however, in general, DMDs should be selected on the basis of factors such as disease severity/activity and patient characteristics, including comorbidities and preference of oral versus parenteral administration [1, 48]. Among the DMDs currently available, few have the convenience of oral administration [46], the most recent being cladribine tablets (Table 2).

A 3.5 mg/kg cumulative dose of cladribine tablets administered in two short courses ≈ 1 year apart reduced clinical relapse (Sect. 5.1), disability progression (Sect. 5.1) and MRI-assessed disease activity (Sect. 5.2) and improved some aspects of HR-QOL (Sect. 5.3) over 96 weeks in adults with RRMS in CLARITY. Consistent with the drug's prolonged lymphocyte-depleting effects (Sect. 2), in the 96-week extension of this study (plus 24 weeks of supplemental follow-up), no additional clinical benefit was gained from continuing versus discontinuing cladribine tablets after the first two annual courses of therapy (Sect. 5.1). As such, cladribine tablets received EU approval for use as a short-course oral treatment administered over a single 2-year period (Sect. 7), which is more convenient than the once- or twice-daily administration needed for other oral DMDs (fingolimod, teriflunomide and dimethyl fumarate) and the relatively frequent injections/infusions needed for most parenteral agents (Table 2). The added convenience of the cladribine tablet regimen may improve therapeutic compliance, although this remains to be formally determined.

Despite the clinical findings of the CLARITY extension, MRI activity was more notable in cladribine tablet recipients who discontinued the drug (i.e. switched

Table 2 Key disease-modifying agents currently available for MS in the EU

Oral agents	**Indication [administration]**
Cladribine	Highly active relapsing MS [2 short courses 1 year apart]
Fingolimod	Highly active relapsing-remitting MS [daily]
Teriflunomide	Relapsing-remitting MS [daily]
Dimethyl fumarate	Relapsing-remitting MS [twice daily]
Parenteral agents	**Indication [administration]**
Interferon-$\beta_{1a,1b}$	Relapsing-remitting MS, relapsing MS, active secondary progressive MS [every 2 days or thrice per week SC or once per week IM]
Peg-interferon-β_{1a}	Relapsing-remitting MS [once every 2 weeks SC]
Glatiramer acetate	Relapsing-remitting MS [daily or thrice per week SC]
Alemtuzumab	Active relapsing-remitting MS [2 short IV courses 1 year apart; ≤ 2 more if needed]
Natalizumab	Highly active relapsing-remitting MS [once every 4 weeks IV]
Ocrelizumab	Active relapsing MS or early primary progressive MS [2 IVs 2 weeks apart, then 1 IV once every 6 months]

IM intramuscular, *IV(s)* intravenous infusion(s), *MS* multiple sclerosis

to placebo) for the extension, although this finding was driven by a subset of patients with the longest bridging interval between CLARITY and entering the extension (Sect. 5.2). However, as the extension was not powered for efficacy and was of limited duration, efficacy data from patients with more prolonged periods without the drug (after having received the two recommended annual treatment courses) would be useful for determining whether the MRI activity seen following discontinuation of cladribine tablets could possibly translate into clinical detriment longer term and whether some patients may benefit from re-treatment.

As mentioned earlier, disease activity is one of the factors used to guide DMD selection [1, 46]. In post hoc analyses of CLARITY and/or the phase 2b ONWARD trial, the benefits of cladribine tablets were seen regardless of patient/disease characteristics, including HDA, with greater benefit evident in patients with, than without, HDA in some instances (Sect. 5.4). On the basis of these analyses, which used various definitions of HDA (including SPMS with relapse; Sect. 5.4), the most suitable population for cladribine tablets approval in the EU was considered to be highly active relapsing MS (Sect. 7) [29]. To further extend these findings, two open-label, single-arm, phase 4 trials will assess the onset of action of cladribine tablets (MAGNIFY-MS) [49] and their impact on HR-QOL (CLARIFY-MS) [50] in this population. Of note, the US FDA has also recently accepted the New Drug Application for cladribine tablets (as a potential treatment for relapsing forms of MS) for filing [51].

All DMDs, whether oral or parenteral, have the potential for tolerability issues, although these can vary greatly in nature and severity [46, 47]. Consequently, tolerability/safety must be considered when selecting a DMD [1] to ensure an appropriate risk/benefit balance [46]. This balance can be achieved via treatment escalation (i.e. a safer agent first, switching later if necessary) or induction (i.e. a highly effective agent used for a short period to quickly gain control of HDA, as a higher serious AE risk may be more justifiable in this setting) [46]. Indeed, cladribine tablets have an acceptable tolerability profile, with lymphopenia being the most common AE (Sect. 6), consistent with its lymphocyte-lowering effects (Sect. 2). However, innate immune system cells seem to be largely spared by cladribine tablets (Sect. 2) and the drug does not appear to be associated with an increased risk of overall infection (although may increase herpes zoster risk; Sect. 6.2) or with an increased risk of malignancy (Sect. 6.3).

Nevertheless, longer-term tolerability data are needed to more definitively determine the potential risks of cladribine tablets, with the mature findings of PREMIERE (a safety registry of MS patients who have participated in cladribine tablet clinical trials; NCT01013350) being awaited with interest. The importance of such data is highlighted by tolerability issues that have emerged during long-term postmarketing surveillance with some of the later DMDs, including natalizumab (PML), fingolimod (e.g. cardiac AEs) and alemtuzumab (e.g. secondary autoimmune disorders), which are issues that have required strategies to optimize patient safety [46, 52].

Two of these DMDs (fingolimod and natalizumab) are indicated specifically for highly active RRMS, whereas cladribine tablets have the broader indication of highly active relapsing MS (Table 2), which encompasses patients with highly active RRMS and SPMS with relapses. Cladribine

tablets are included in current ECTRIMS/EAN guidelines as an option for the treatment of active SPMS (which can be with relapses and/or new MRI activity [2]), with the other options being ocrelizumab, interferon-$\beta_{1a,1b}$ and mitoxantrone (recommendation is weak for each) [1]. In addition, NICE technology appraisal guidance recommends cladribine tablets for the treatment of adults with highly active RRMS (i.e. that is rapidly evolving and severe or is responding inadequately to other DMDs) and considers alemtuzumab, fingolimod and natalizumab to be among the most appropriate comparators [53].

Guidelines from the Association of British Neurologists (written prior to approval of cladribine tablets) categorize DMDs into 'moderately effective' (interferon-β, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod) and 'highly effective' (alemtuzumab, natalizumab), although direct comparisons are sparse [54], leaving their relative efficacy and tolerability of some debate. Cladribine tablets have not been directly compared with other DMDs, although various indirect comparisons have been conducted [55–59]; however, given the indirect nature of these comparisons, their findings require cautious interpretation and robust head-to-head trials would be beneficial.

As some patients require a sequence of treatments for disease control maintenance or a change in DMD for reasons such as intolerable side effects [46], studies assessing the feasibility of switching between cladribine tablets and other DMDs are of interest, particularly given the long-lasting immunological effects of cladribine tablets and agents such as alemtuzumab and ocrelizumab [46] and thus the potential for additive effects [5]. In this regard, a post hoc analysis of data from CLARITY, its extension and PREMIERE found that 22% of the 576 assessed recipients of cladribine tablets 3.5 mg/kg were treated with a subsequent DMD, most commonly interferon-β_{1a} and glatiramer acetate [60]; similar analyses specifically in patients with HDA would be of interest.

MS carries a high economic burden, with costs increasing with worsening disease [61]. Resource consumption data collected during CLARITY indicate that cladribine tablets are likely to be of economic benefit in MS [62]. Cladribine tablet recipients generally used fewer healthcare and societal resources than placebo recipients during the 96-week trial, with health resource benefits also being evident with the drug in patients with HDA [62]. Further pharmacoeconomic data from a cost-utility analysis indicate that cladribine tablets may dominate (i.e. be more effective and less costly than) alemtuzumab and natalizumab in HDA RRMS patients from the perspective of the NHS in England [63], with cost-effectiveness data reported in the NICE technology appraisal guidance generally supporting these findings [53]. Additional pharmacoeconomic studies are awaited.

In conclusion, although active comparisons and longer-term follow-up would be beneficial, current data indicate that for adults with highly active relapsing MS, cladribine tablets are an effective oral treatment option, with an acceptable tolerability profile and the convenience of low-burden, short-course administration.

Data Selection Cladribine: 533 records identified	
Duplicates removed	104
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	316
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	50
Cited efficacy/tolerability articles	18
Cited articles not efficacy/tolerability	45
Search Strategy: EMBASE, MEDLINE and PubMed from 2014 to present. Previous Adis Drug Evaluation published in 2014 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Cladribine, Mavenclad, 2-Chlorodeoxyadenosine, 2-CdA, multiple sclerosis, RRMS, relapsing MS, remitting MS. Records were limited to those in English language. Searches last updated 27 July 2018	

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Compliance with Ethical Standards

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