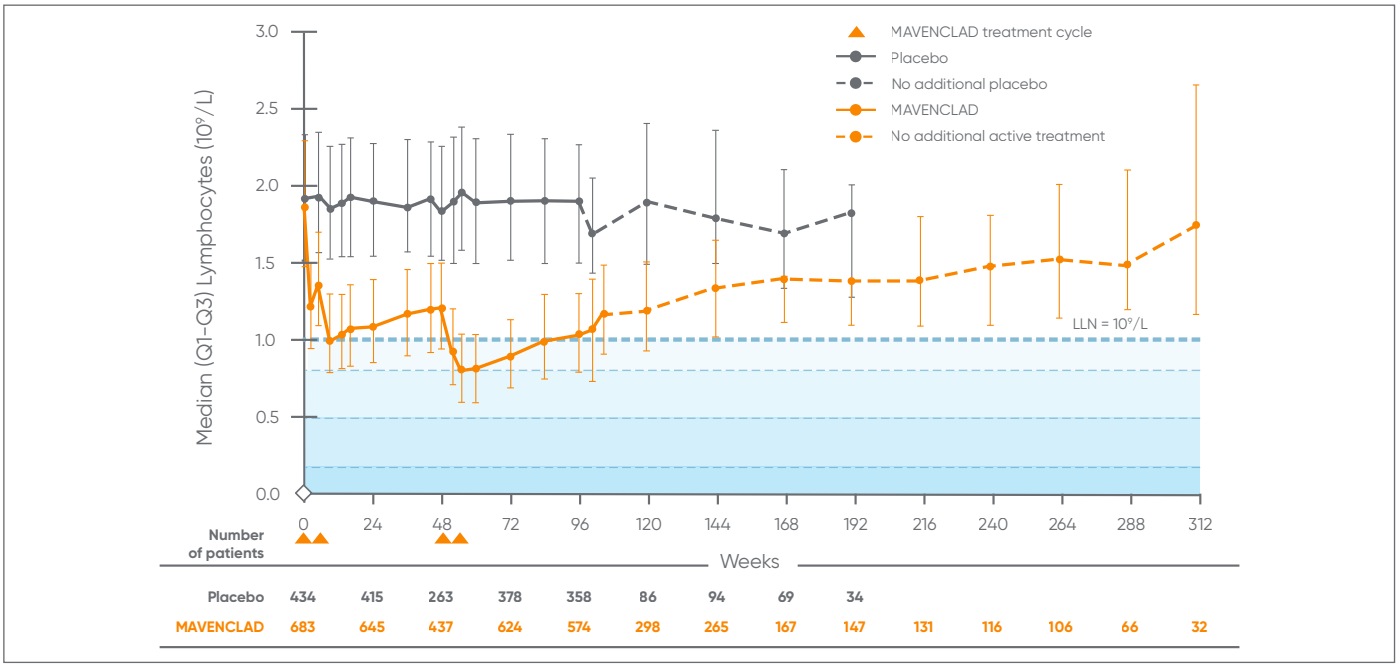
How MAVENCLAD Works: Proposed Mechanism of Action

The mechanism of action by which MAVENCLAD exerts its therapeutic effects in patients with multiple sclerosis (MS) is not fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes.[1]

MAVENCLAD selectively depletes lymphocytes. After 2 months, most immune cells begin to recover towards normal levels[2-4]*



*Pooled data from CLARITY, CLARITY EXT, and PREMIERE.

LLN, lower limit of normal; Q, quartile.

PREMIERE: Prospective Observational Long-Term Safety Registry of Multiple Sclerosis Patients who have participated in oral cladribine clinical trials.

CLARITY Extension: Long-term safety and tolerability of oral cladribine in patients who have previously completed treatment in the pivotal CLARITY trial.

INDICATION and IMPORTANT SAFETY INFORMATION for MAVENCLAD® (cladribine) tablets

MAVENCLAD® (cladribine) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS.

Limitations of Use: MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

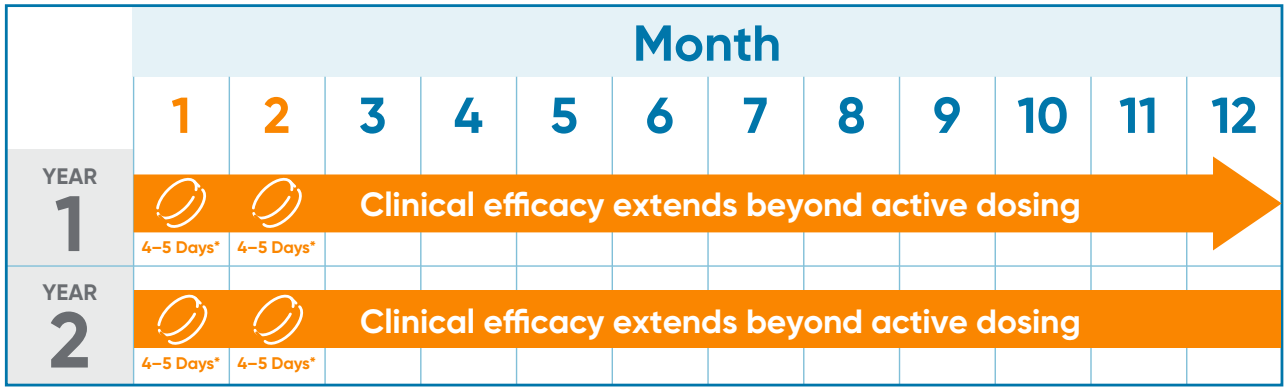
IMPORTANT SAFETY INFORMATION

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.**
- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant.**

Please see Important Safety Information throughout this piece, and click **here** to view full Prescribing Information, including **BOXED WARNING**.

MAVENCLAD is the first and only short-course oral therapy with no more than 10 treatment days a year for 2 years[1,5]



MAVENCLAD is eliminated from the body 1 week after administration,[1,6] while the efficacy of MAVENCLAD is sustained beyond active dosing.[5]

*1 or 2 tablets per day depending on body weight.

Screening and monitoring should be performed before, during, and after treatment. No additional doses of MAVENCLAD are to be administered during the next 2 years as treatment during the next 2 years may further increase the risk of malignancy.[1]

IMPORTANT SAFETY INFORMATION (CONTINUED)

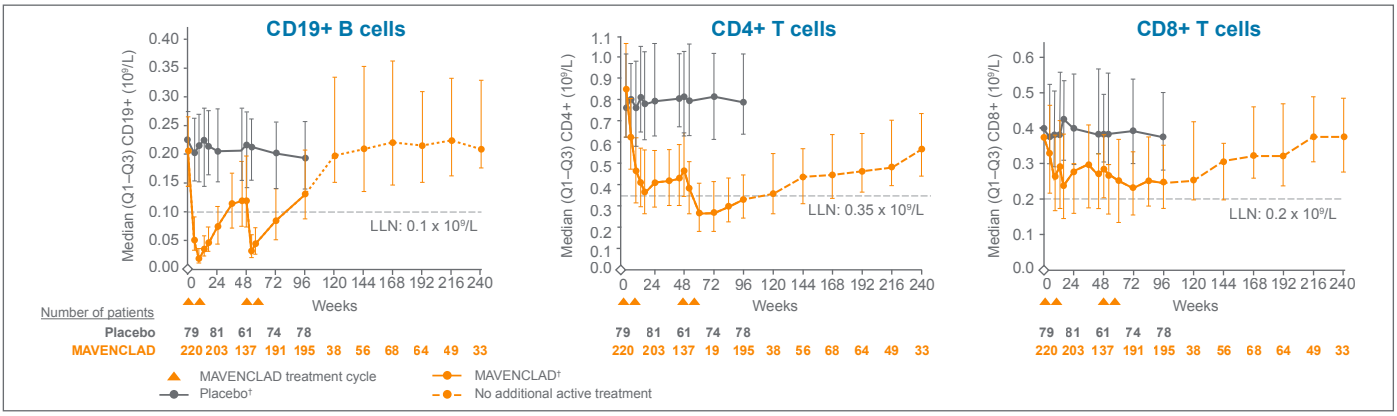
CONTRAINDICATIONS

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients infected with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.
- Women intending to breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose.

WARNINGS AND PRECAUTIONS

- **Malignancies:** Treatment with MAVENCLAD may increase the risk of malignancy. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.
- **Risk of Teratogenicity:** MAVENCLAD may cause fetal harm when administered to pregnant women. In females of reproductive potential, exclude pregnancy before initiation of each treatment course of MAVENCLAD and prevent by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment.
- **Lymphopenia:** MAVENCLAD causes a dose-dependent reduction in lymphocyte count. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before, during, and after treatment.

MAVENCLAD selectively depletes B cells, and to a lesser extent, T cells, while leaving the innate immune system relatively intact[4,7*]



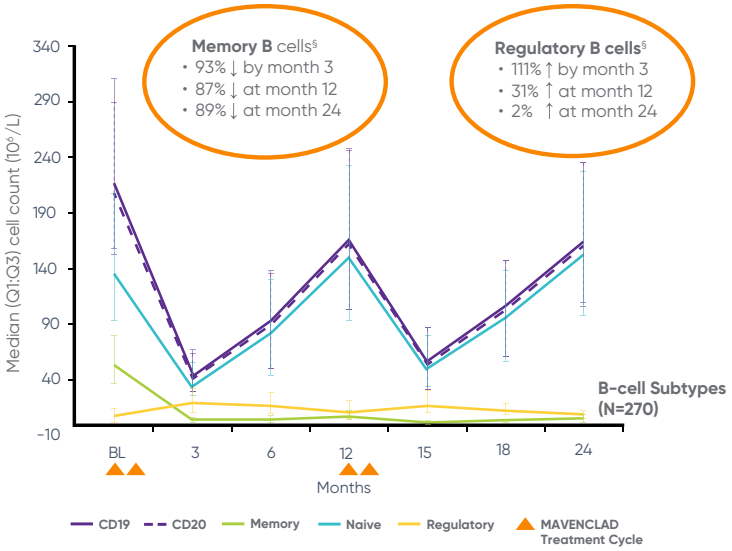
*Pooled data from CLARITY, CLARITY EXT, and PREMIERE. †MAVENCLAD/placebo were administered as 2 courses separated by 1 year (a maximum of 20 days of treatment). Each course consisted of 2 treatment weeks: 1 at the beginning of the first month and 1 at the beginning of the second month. Data from patients randomized to placebo in CLARITY or who received a cumulative dose of MAVENCLAD for 2 years in CLARITY or CLARITY EXT were included. Any relevant follow-up in CLARITY EXT and PREMIERE are also reported.[4]

Limitations: This data includes bridging intervals between CLARITY, CLARITY Ext, and PREMIERE during which lymphocyte counts were not monitored. Patients receiving IFN-beta as rescue therapy (n=11) were not excluded or censored.

MAVENCLAD has a mild-to-moderate effect on neutrophils and monocytes.[3,8]

With MAVENCLAD, median counts of natural killer cells, monocytes, and CD8+ cytotoxic T cells remained within the normal range throughout the treatment period.[3,4,8,9]

MAGNIFY-MS Substudy‡: Additional Data Showing Reduction and Recovery Patterns of B-cell Subsets in Patients Treated With MAVENCLAD Over 24 Months[7§]



Study Limitations

- MAGNIFY-MS was a Phase IV, open-label, single-arm, multicenter study
- The primary endpoint of MAGNIFY-MS was to determine the onset of action of MAVENCLAD in patients with highly active relapsing MS¶
- The data presented here are based on a poster that has not been peer-reviewed

Due to the study limitations listed above, no definitive conclusions of efficacy can be drawn from these results and no treatment decisions should be made from these data.

‡MAGNIFY-MS was a Phase IV, open-label, single-arm, multicenter, 2-year study to determine the onset of action of MAVENCLAD, as measured by combined unique active lesions. These data illustrate the longitudinal evaluation of peripheral blood immune cells in patients receiving MAVENCLAD. Patients with highly active relapsing MS (N=270) received 2 courses of active treatment (week 1 and week 5 of year 1, week 1 and week 5 of year 2).

§Median percentage change from baseline.

¶Highly active relapsing MS was defined by having 1 relapse in the previous year and ≥1 T1-Gd+ lesion, or ≥9 T2 lesions, while on therapy with other DMTs, or ≥2 relapses in the previous year, whether on DMT treatment or not.

BL, baseline; DMT, disease-modifying therapy.

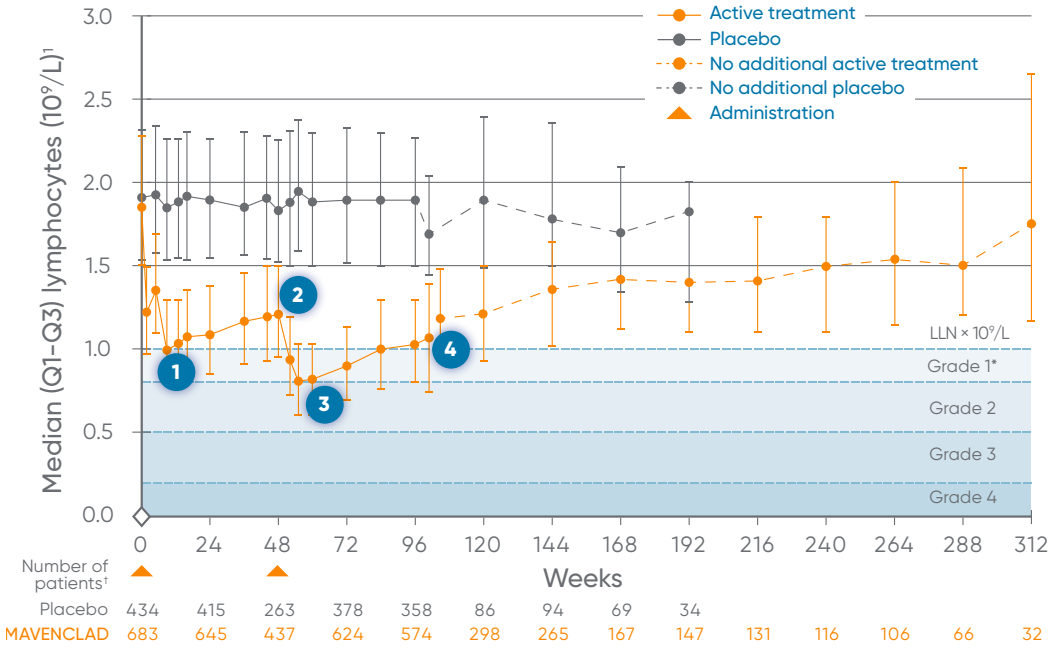
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Effect of MAVENCLAD on total lymphocytes

Lymphocyte counts were measured as part of routine clinical laboratory evaluations in patients in clinical studies. MAVENCLAD causes a dose-dependent reduction in lymphocyte count.[3] In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course.[1]

In patients treated with MAVENCLAD as monotherapy, lymphopenia observed was transient and mostly mild to moderate. The median duration of severe lymphopenia was 6.0 weeks to improvement to Grade ≤2 and 28.1 weeks to recovery to Grade ≤1. 26% and 1% of patients had nadir absolute lymphocyte counts less than 500 and less than 200 cells/µL, respectively. At the end of the second treatment course, 2% of clinical study patients had lymphocyte counts less than 500 cells per microliter.[1]



Terminal half-life
~24 hours[1,6]

Elimination
~1 week[1,7]

Post hoc analysis, percentage of patients who had median ALC at Grade 1 lymphopenia or within normal limits[4‡§]:

1 Week 13 of year 1
- Normal to grade 1: **82.2%**
- Grade 2: 16.4%
- Grade 3: 1.3%
- Grade 4: 0.0%

2 Week 48 of year 1
- Normal to grade 1: **89.1%**
- Grade 2: 10.9%
- Grade 3: 0.0%
- Grade 4: 0.0%

3 Week 12 of year 2
- Normal to grade 1: **64.5%**
- Grade 2: 28.9%
- Grade 3: 6.7%
- Grade 4: 0.0%

4 Week 48 of year 2
- Normal to grade 1: **88.3%**
- Grade 2: 10.4%
- Grade 3: 1.3%
- Grade 4: 0.0%

***Grade 1, <LLN–800/µL; grade 2, <800–500/µL; grade 3, <500–200/µL; grade 4, <200/µL.[11]**

†Visits with sample size ≥30 are displayed.[4]

‡Data were derived from a post hoc analysis of the 2 courses in patients receiving MAVENCLAD in CLARITY.[4]

§Percentages were calculated as a proportion of all patients with laboratory values at each time point A total of 1.7% of patients (3/176) experienced ≥1 episode of grade 4 lymphopenia at any time point during the entire trial period.[4]

ALC: absolute lymphocyte count; LLN: lower limit of normal; RMS: relapsing multiple sclerosis.

Please see Important Safety Information throughout this piece, and click **here** to view full Prescribing Information, including **BOXED WARNING**.

Adverse Reactions in CLARITY With an Incidence of ≥5% for MAVENCLAD and Higher Than Placebo[1]

Adverse Reaction	Placebo (n=435), %	MAVENCLAD (n=440), %
Upper respiratory tract infection	32	38
Headache	19	25
Lymphopenia	2	24
Nausea	9	10
Back pain	6	8
Arthralgia and arthritis	5	7
Insomnia	4	6
Bronchitis	3	5
Hypertension	3	5
Fever	3	5
Depression	3	5

Discontinuation Rate Due to Adverse Reactions

In the pivotal trial, **3.5%** of patients receiving MAVENCLAD discontinued treatment due to adverse reactions (ARs) vs **2.1%** of patients receiving placebo.[5]

The most common ARs with an incidence of >20% reported in CLARITY were upper respiratory tract infection, headache, and lymphopenia. In clinical studies, 11% of MAVENCLAD patients had hypersensitivity ARs, compared with 7% of placebo patients.[1]

89,000+ patients have been treated globally in the real-world setting for a total of 203,000+ patient-years



Confirmed cases of progressive multifocal leukoencephalopathy (PML) have been reported in up to 8 years of safety follow-up with patients with MS treated with MAVENCLAD

In patients treated with parenteral cladribine for oncological indications, cases of PML have been reported in the postmarketing setting.[1]



Increase in risk of secondary autoimmune diseases vs placebo

In the all-exposed cohort, the incidence of autoimmune diseases was similar between the MAVENCLAD group (0.58 events per 100 patient-years) and the placebo group (0.73 events per 100 patient-years).[1,12,13]

IMPORTANT SAFETY INFORMATION (CONTINUED)

- **Infections:** Serious, including life-threatening or fatal, infections have occurred. MAVENCLAD reduces the body's immune defense and an increased risk of infections has been observed in patients receiving MAVENCLAD. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies; serious or severe infections occurred in 2.4% of MAVENCLAD-treated patients and 2.0% of placebo-treated patients. The most frequent serious infections included herpes zoster and pyelonephritis. Fungal infections were observed, including cases of coccidioidomycosis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program.
  - Screen patients for active and latent infections (tuberculosis, hepatitis B or C). Delay treatment until infection is fully resolved or controlled.
  - Vaccinate patients who are seronegative for varicella zoster virus (VZV) prior to treatment. Vaccinate patients who are seropositive to VZV with recombinant, adjuvanted zoster vaccine either prior to or during treatment, including when their lymphocyte counts are less than or equal to 500 cells per microliter.
  - Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections.
  - Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with parenteral cladribine for oncologic indications. No case of PML has been reported in clinical studies of cladribine in patients with MS. Obtain a baseline magnetic resonance imaging (MRI) within 3 months before initiating the first treatment course of MAVENCLAD. At the first sign of PML, withhold MAVENCLAD and perform an evaluation.
  - Administer all immunizations (except as noted for VZV) according to immunization guidelines prior to starting MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD due to risk of infection.

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Proposed mechanism of action for MAVENCLAD

- MAVENCLAD selectively depletes B cells, and to a lesser extent, T cells, while leaving the innate immune system relatively intact[4*]
- Two months after MAVENCLAD administration, most immune cells begin to recover toward normal levels, while memory B cells remain depleted for up to 12 months after MAVENCLAD treatment[7]

Learn more at MAVENCLAD.com/HCP

*Pooled data from CLARITY, CLARITY EXT, and PREMIERE.

IMPORTANT SAFETY INFORMATION (CONTINUED)

- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Graft-versus-Host Disease with Blood Transfusions:** Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications. In patients who require blood transfusion, irradiation of cellular blood components is recommended.
- **Liver Injury:** In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) compared to 0 placebo patients. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment. Discontinue if clinically significant injury is suspected.
- **Hypersensitivity:** If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.
- **Cardiac Failure:** In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis. Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., shortness of breath, rapid or irregular heartbeat, swelling).

Adverse Reactions: The most common adverse reactions (incidence of >20%) are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions: Concomitant use with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Acute short-term therapy with corticosteroids can be administered. Monitor for additive effects on the hematological profile with use of hemotoxic drugs. Avoid concomitant use of antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Use in Specific Populations: Studies have not been performed in pediatric, or elderly patients >65 years, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono, Inc. at **1-800-283-8088 ext. 5563** or FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**.

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References:

1. MAVENCLAD [prescribing information]. Rockland, MA: EMD Serono, Inc; 2024. **2.** Multiple Sclerosis Association of America (January 2023). Approved Long-term treatments for MS. My MSAA. Retrieved April 3, 2023. https://mymsaa.org/PDFs/Treatment_Chart.pdf **3.** Baker D, Herrod SS, Alvarez-Gonzalez C, Zalewski L, Albor C, Schmierer K. Both cladribine and alemtuzumab may effect MS via B-cell depletion. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(4):e360. **4.** Comi G, Cook S, Giovannoni G, et al. Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis. *Mult Scler Relat Disord*. 2019;29:168-174. **5.** Giovannoni G, Comi G, Cook S, et al. For the CLARITY Study Group. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):416-426. **6.** Leist TP, Weissert R. Cladribine: mode of action and implications for treatment of multiple sclerosis. *Clin Neuropharmacol*. 2011;34(1):28-35. **7.** Wiendl H, De Stefano N, Barkhof F, et al. Blood biomarker dynamics in highly active relapsing multiple sclerosis patients treated with cladribine tablets: results of the 2-year MAGNIFY MS Study. Poster presented at: Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) 2023 Forum; February 23-25, 2023. **8.** Soelberg-Sorensen P, Dangond F, Hicking C, Giovannoni G. Innate immune cell counts in patients with relapsing–remitting multiple sclerosis (RRMS) treated with cladribine tablets 3.5 mg/kg in CLARITY and CLARITY Extension. Poster presented at: Third Annual Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2018 [P061]; February 1-3, 2018; San Diego, CA. **9.** Rieckmann P, Comi G, Cook S, et al. Effects of cladribine tablets on peripheral lymphocyte subtypes implicated in multiple sclerosis immunopathogenesis: surface marker analysis for a subset of patients from the 96-week, phase III, double-blind, placebo-controlled CLARITY study. Poster presented at: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); September 9-12, 2009; Dusseldorf, Germany. **10.** Sigal DS, et al. Beyond hairy cell: the activity of cladribine in other hematologic malignances. *Blood*. 2010;116(16):2884-2896. **11.** Common Terminology Criteria for Adverse Events (CTCAE) v5.0. November 27, 2017. **12.** Data on file. Merck KGaA, Darmstadt, Germany. **13.** Merck KGaA. European Commission grants approval for Mavenclad (cladribine tablets). Published August 25, 2017. Accessed August 21, 2019. https://www.emdgroup.com/en/news/mavenclad-25-08-2017.html

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