MAVENCLAD®
(cladribine) tablets 10 mg

MAVENCLAD PROPOSED MOA AND ITS EFFECT ON THE IMMUNE SYSTEM

INDICATION

MAVENCLAD® (cladribine) tablets 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

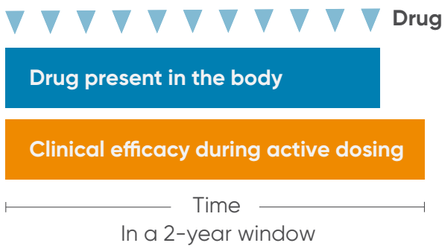
- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard 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 on pages 12-13 and accompanying full Prescribing Information, including **boxed WARNING.**

THE IMMUNE SYSTEM AND RMS TREATMENTS

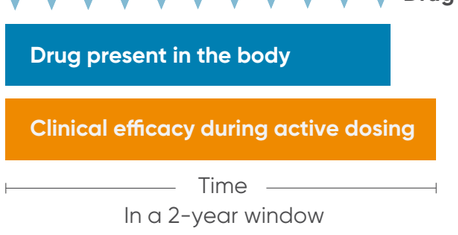
In RMS, there are multiple treatment approaches to consider[1]

Immunomodulation[1,2]



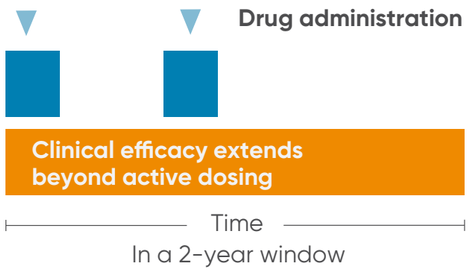
- Continuous administration
- Ongoing modulation of immune function during active treatment without immunodepletion

Chronic immunosuppression[2]



- Continuous administration
- Ongoing suppression of immune function during active treatment

Immunodepletion followed by repopulation[2,3]



- Therapy administered intermittently as a short course
- Dosing followed by depletion and repopulation

Adaptive and innate immune cells play a major role in MS[4]

Innate immune cells

Innate immune cells serve as immune surveillance and are the first line of defense

NK cells

- Induce apoptosis in virus-infected cells[4]
- May play a role **in MS** pathogenesis[5]

Neutrophils

- Phagocytose bacteria and fungi[4]
- The role of neutrophils **in MS** is still emerging[6]

Monocytes
(macrophages and dendritic cells)

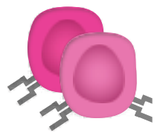
- Phagocytose pathogens and present antigens[4]
- May have a pro-inflammatory role **in MS**[7]

Adaptive immune cells

Adaptive immune cells are the second line of defense and are key drivers of neuroinflammation in MS[4,7,8]

B cells

- Differentiate into antibody-secreting plasma B cells, including in response to vaccines[4]
- **In MS**, can produce antibodies that lead to myelin damage and also present antigen to activate T cells[9,10]



CD4+ T-helper cells, CD8+ cytotoxic T cells

- Attack cells (eg, virus/bacteria-infected cells, tumor cells), able to respond to re-exposure quickly[4]
- Help regulate the immune response and release pro-inflammatory proteins
- **In MS**, contribute to CNS inflammation and damage and also do not function correctly and are widely implicated as pro-inflammatory cells[7,8]

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 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 while taking MAVENCLAD tablets and for 10 days after the last dose.

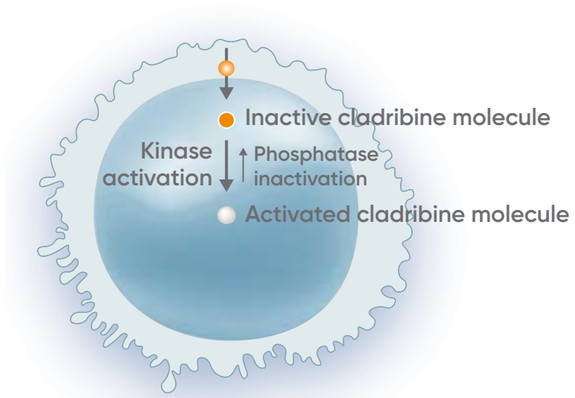
Please see Important Safety Information on pages 12-13 and accompanying full Prescribing Information, including **boxed WARNING**.

MAVENCLAD® (cladribine) tablets 10 mg

MAVENCLAD IS ASSOCIATED WITH A REDUCTION AND SUBSEQUENT RECOVERY IN LYMPHOCYTE COUNT[11-13]

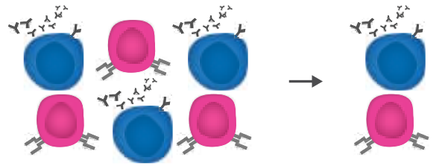
MAVENCLAD is thought to preferentially target B and T lymphocytes

MAVENCLAD is a prodrug that is preferentially active in B and T lymphocytes



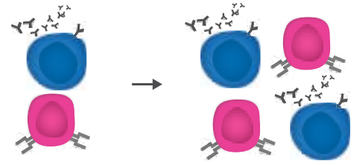
- MAVENCLAD is a prodrug that is activated by specific kinases and deactivated by specific phosphatases. MAVENCLAD becomes active in the cells upon phosphorylation to its 2-chlorodeoxyadenosine triphosphate (Cd-ATP) metabolite[14]
- Activated MAVENCLAD accumulates in B and T lymphocytes because they have a higher kinase-to-phosphatase ratio than other cells and this leads to cell death through apoptosis.[12,15]

Reduction of B and T lymphocytes



- Apoptosis plays a significant role in controlling the immune response and the deletion of immune cells recognizing self-antigens[16]
- The mechanism by which MAVENCLAD exerts its therapeutic effects in 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[14]
- Its targeted effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS[12]
- In addition to lymphopenia, decreases in other blood cells and hematological parameters (neutrophils, hemoglobin, and platelets) have been reported with MAVENCLAD in clinical studies[14]

Recovery of B and T lymphocytes



- Lymphocytes generally recovered over several months or more. Lymphocyte reduction and recovery is shown on the next page[14]
- **MAVENCLAD** has an estimated terminal half-life of approximately **24 hours** and is eliminated from the body in **≈1 week**[12,14,17]

Images are for illustrative purposes only.

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. 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. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.

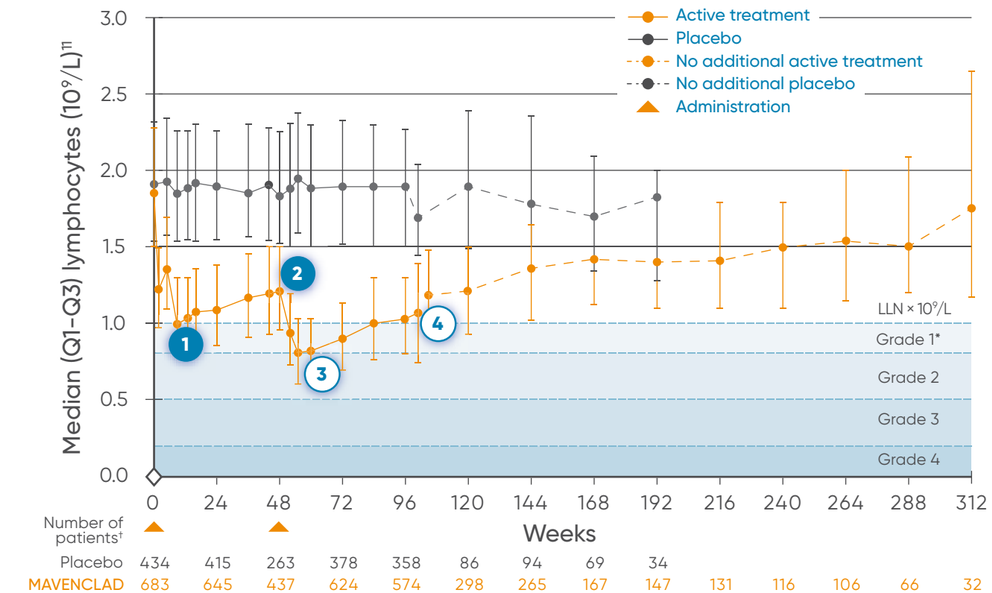
Please see Important Safety Information on pages 12-13 and accompanying full Prescribing Information, including **boxed WARNING**.

EFFECT OF MAVENCLAD ON TOTAL LYMPHOCYTES

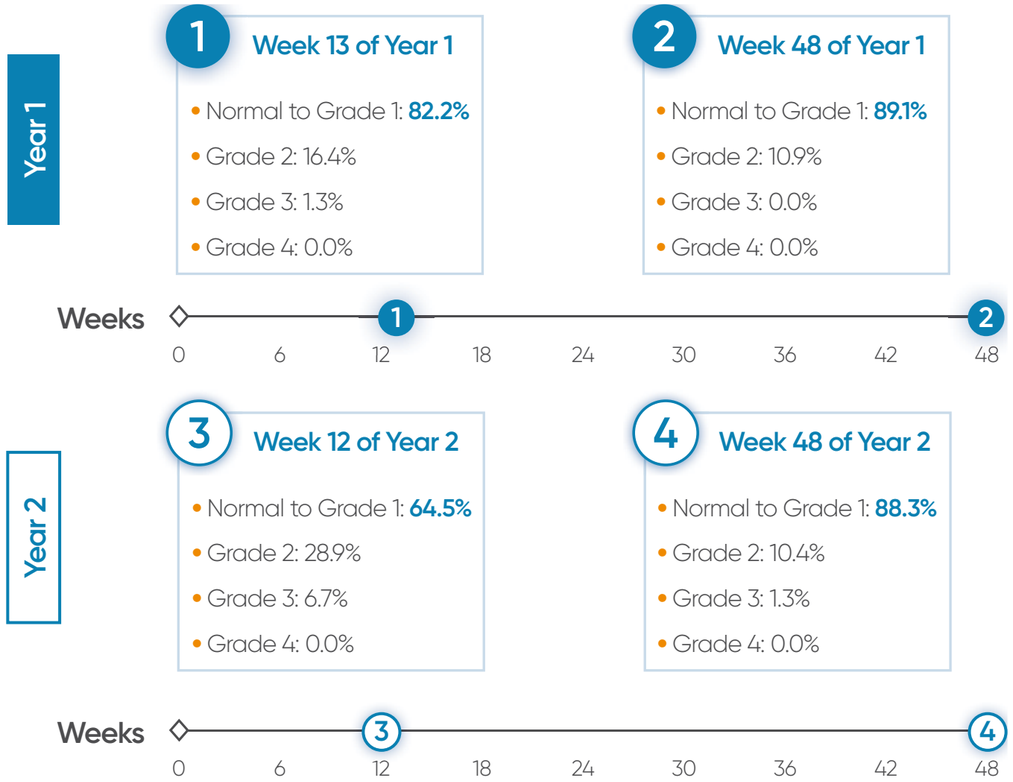
Lymphocyte counts were measured as part of routine clinical laboratory evaluations in patients in clinical studies. MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course.[14,17]

In patients treated with MAVENCLAD as monotherapy, lymphopenia observed was 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.[14,18]

If necessary, delay the second treatment course for up to 6 months to allow recovery of lymphocytes to at least 800 cell/uL. If this recovery takes more than 6 months, the patient should not receive further treatment with MAVENCLAD.



Post hoc analysis, percentage of patients who had median ALC at Grade 1 lymphopenia or within normal limits[11‡§]:



*Grade 1 <LLN-800/µL; 2, <800-500/µL; 3, <500-200/µL; 4, <200/µL.[19]
†Visits with sample size ≥30 are displayed.[11]
‡Data were derived from a post hoc analysis of the 2 courses in patients receiving MAVENCLAD in CLARITY.
§Percentages were calculated as a proportion of all patients with laboratory values at each time point.[11]

ALC: absolute lymphocyte count; CLAdRIbine Tablets treating multiple sclerosis orallY; LLN: lower limit of normal.

WARNINGS AND PRECAUTIONS (cont.)

- **Infections:** MAVENCLAD can reduce the body's immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.
- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of 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.

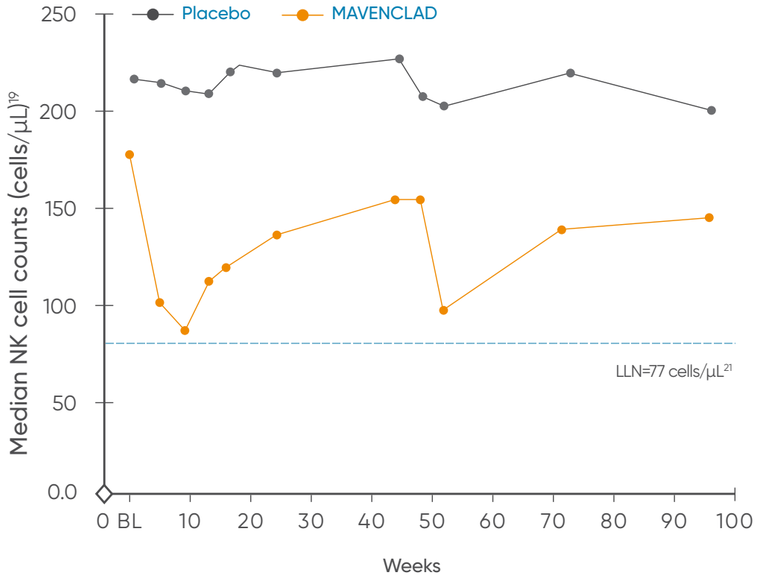
Please see Important Safety Information on pages 12-13 and accompanying full Prescribing Information, including **boxed WARNING**.

TREATMENT WITH MAVENCLAD HAD THE FOLLOWING RESULTS ON SELECT INNATE AND ADAPTIVE IMMUNE CELLS

Post-hoc analysis: median levels of NK cells remained within normal limits throughout MAVENCLAD treatment[20]*

NK cells[4]

Induce apoptosis in virus-infected cells



- Reduction in median NK cell counts followed by recovery, but median cell counts remained within normal limits throughout treatment[20]

- Decreases in blood cells, other than lymphocytes, and hematological parameters have been reported with MAVENCLAD in clinical studies[14]
- In general, mild-to-moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed[14]
  - Severe decreases in neutrophil counts were observed in 3.6% of patients treated with MAVENCLAD, compared with 2.8% of placebo patients

*204 patients from a post hoc analysis of CLARITY ([n=98] placebo, [n=101] MAVENCLAD) had lymphocytes and additional blood cells analyzed.[20]

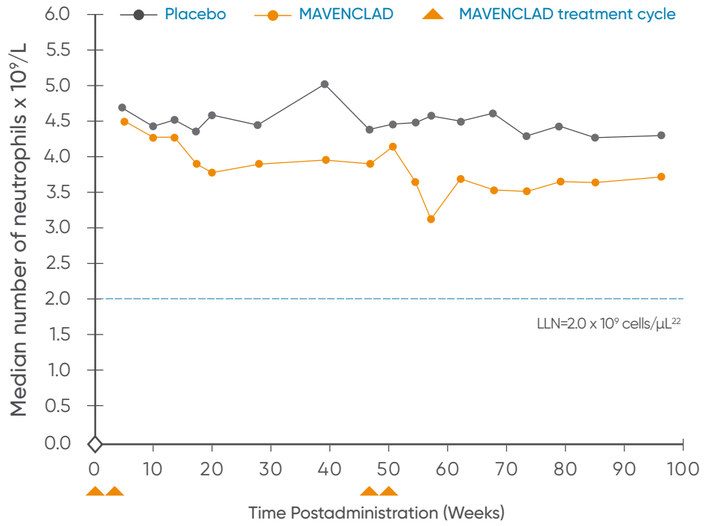
WARNINGS AND PRECAUTIONS (cont.)

- **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:** In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

Post hoc analysis: median levels of neutrophils and monoyctes remained within normal limits throughout MAVENCLAD treatment[3,13†]

Neutrophils[4]

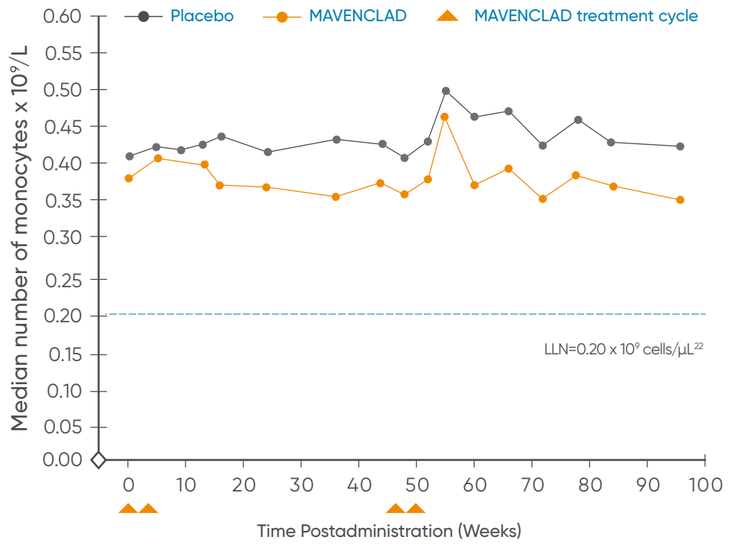
Phagocytose bacteria and fungi



- Mild-to-moderate effect on neutrophils[3,13]
- Median cell counts remained within normal range throughout the treatment period[3,13]

Monocytes[4]

Phagocytose pathogens and present antigens



- Mild-to-moderate effects on platelets and monocytes[3,13]
- Median cell counts remained within normal range throughout the treatment period[3,13]

†Post hoc analysis of patients taking MAVENCLAD (n=103) and placebo (n=101) from CLARITY had lymphocytes and additional blood cells analyzed.[3,13]

CLAdRIbine Tablets treating multiple sclerosis orallY; LLN: lower limit of normal.

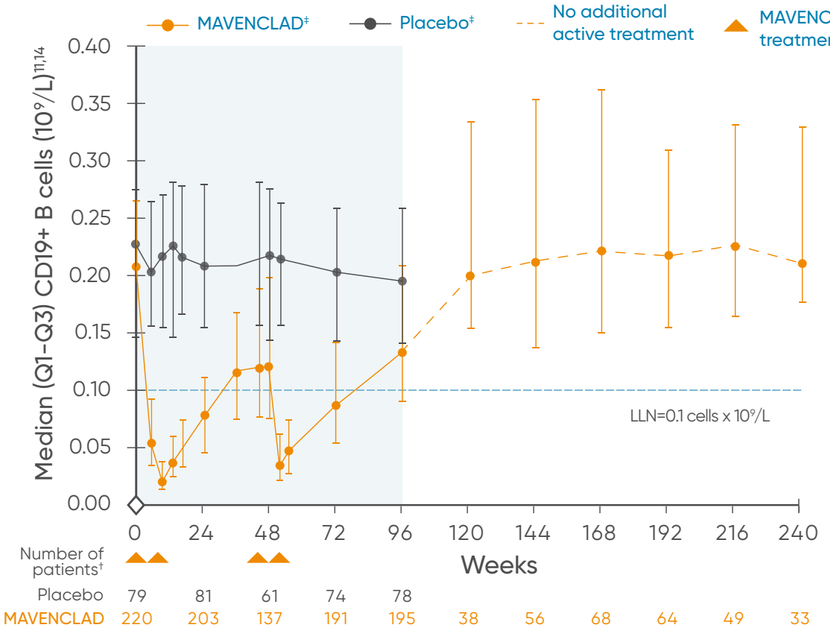
Please see Important Safety Information on pages 12–13 and accompanying full Prescribing Information, including **boxed WARNING**.

MAVENCLAD® (cladribine) tablets 10 mg

Pooled clinical trial data: MAVENCLAD treatment resulted in sharper depletion, followed by recovery, of CD19+ B cells, compared to T cells[3,11*†]

B cells[9,10]

In MS, can produce antibodies that lead to myelin damage and present antigen to activate T cells



*Pooled data from CLARITY, CLARITY EXT, and PREMIERE.[11]
†Median CD19+ B cells reached a nadir at 2 months (median 0.018 × 10⁹ cells/L) and then gradually increased.[11]
‡MAVENCLAD and 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.[11,14]

WARNINGS AND PRECAUTIONS (cont.)

- **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.

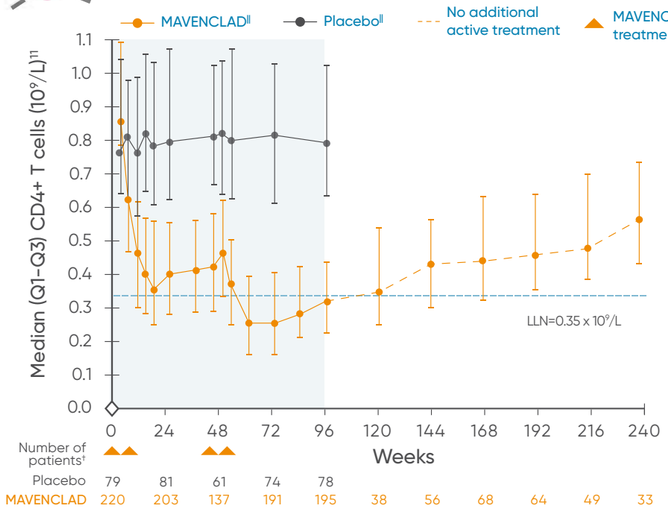
Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD 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.

Pooled clinical trial data: CD4+ cells were more sensitive to MAVENCLAD than CD8+ cells and median CD8+ T-cell counts remained within normal range[11§]

CD4+ helper T cells[8]

In MS, do not function correctly and are widely implicated as pro-inflammatory cells

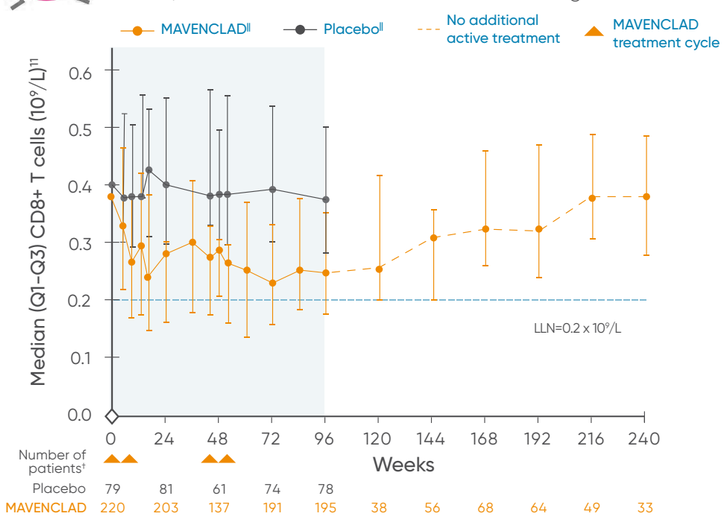


Reduction in T cells[11]

- Median CD4+ T-cell counts decreased followed by recovery

CD8+ cytotoxic T cells[8]

In MS, contribute to CNS inflammation and damage



- Median CD8+ T-cell counts decreased but remained above the lower limit of normal[11]

§Pooled data from CLARITY, CLARITY EXT, and PREMIERE.[11]
‖MAVENCLAD and 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.[11]

CLAdRIbine Tablets treating multiple sclerosis orallY; LLN: lower limit of normal.

Please see Important Safety Information on pages 12-13 and accompanying full Prescribing Information, including **boxed WARNING**.

IMPORTANT SAFETY INFORMATION

INDICATION

MAVENCLAD® (cladribine) tablets 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**

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 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 while taking MAVENCLAD tablets 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. 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. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** MAVENCLAD can reduce the body's immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.
- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of 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.
- **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:** In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. 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.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD 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.

Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

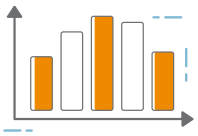
Use in Specific Populations: Studies have not been performed in pediatric or elderly patients, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

Please see the accompanying full Prescribing Information, including **boxed WARNING** for additional information.

Scan me

Find additional helpful content on the MAVENCLAD website

Full Dosing Guide



Efficacy

Safety

REFERENCES:

1. Giovannoni G. Disease-modifying treatments for early and advanced multiple sclerosis: a new treatment paradigm. *Curr Opin Neurol*. 2018;31(3):233-243. **2.** Soelberg-Sorensen P, Sellebjerg F. Pulsed immune reconstitution therapy in multiple sclerosis. *Ther Adv Neurol Disord*. 2019;12:1756286419836913. **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.** Warrington R, Watson W, Kim HL, Antonetti FR. An introduction to immunology and immunopathology. *Allergy Asthma Clin Immunol*. 2011;7:S1. **5.** Gross CC, Schulte-Mecklenbeck A, Wiendl H, et al. Regulatory functions of natural killer cells in multiple sclerosis. *Front Immunol*. 2016;7:606. **6.** Woodberry T, Bouffler SE, Wilson AS, Buckland RL, Brüstle A. The emerging role of neutrophil granulocytes in multiple sclerosis. *J Clin Med*. 2018;7(12):511. **7.** Nally FK, De Santi C, McCoy CE. Nanomodulation of macrophages in multiple sclerosis. *Cells*. 2019;8(6):543. **8.** Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol*. 2015;15(9):545-558. **9.** Disanto G, Morahan JM, Barnett MH, Giovannoni G, Ramagopalan SV. The evidence for a role of B cells in multiple sclerosis. *Neurology*. 2012;78:823-832. **10.** Krumbholz M, Derfuss T, Hohlfeld R, Meinl E. B cells and antibodies in multiple sclerosis pathogenesis and therapy. *Nat Rev Neurol*. 2012;8(11):613-623. **11.** 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. **12.** Leist TP, Weissert R. Cladribine: mode of action and implications for treatment of multiple sclerosis. *Clin Neuropharmacol*. 2011;34(1):28-35. **13.** Soelberg-Sorensen PS, et al. Innate immune cell counts in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets 3.5 mg/kg in CLARITY and CLARITY EXT. 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. **14.** MAVENCLAD Prescribing Information. EMD Serono, Inc. 2019. **15.** Ceronie B, Jacobs BM, Baker D, et al. Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. *J Neurol*. 2018;265(5):1199-1209. **16.** Ekert PG, Vaux DL. Apoptosis and the immune system. *Br Med Bull*. 1997;53(3):591-603. **17.** Benet LZ, Zia-Amirhosseini P. Basic principles of pharmacokinetics. *Toxicol Pathol*. 1995;23(2);115-123. **18.** Data on file (NDA, Summary of clinical safety). **19.** CTCAE Version 5, November 17, 2017. **20.** 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. **21.** Bisset LR, Lung TL, Kaelin M, Ludwig E, Dubs RW. Reference values for peripheral blood lymphocyte phenotypes applicable to the healthy adult population in Switzerland. *Eur J Haematol*. 2004;72(3):203-212. **22.** Haematology normal adult reference ranges. NHS. Updated May 19, 2017. Accessed October 27, 2020. https://www.royalwolverhampton.nhs.uk/services/service-directory-a-z/pathology-services/departments/haematology/haematology-normal-adult-reference-ranges/.

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 on pages 12-13 and accompanying full Prescribing Information, including **boxed WARNING**.

EMD SERONO

EMD Serono, Inc. One Technology Place, Rockland, MA 02370
US-MAV-00593 11/20

MAVENCLAD® (cladribine) tablets 10 mg