MAVENCLAD®
(cladribine) tablets 10 mg

DOSING GUIDE

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 A SHORT-COURSE ORAL TREATMENT[1]

MAVENCLAD is the first and only short-course oral treatment with proven efficacy, convenient dosing, and 20+ years of safety data[1-3]*

Convenient dosing schedule[1]

MAVENCLAD is administered in 2 treatment courses approximately 1 year apart

The recommended cumulative dosage of MAVENCLAD is 3.5 mg/kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg/kg per treatment course).

Each treatment course is divided into 2 treatment cycles[1]:

Year 1 treatment course:

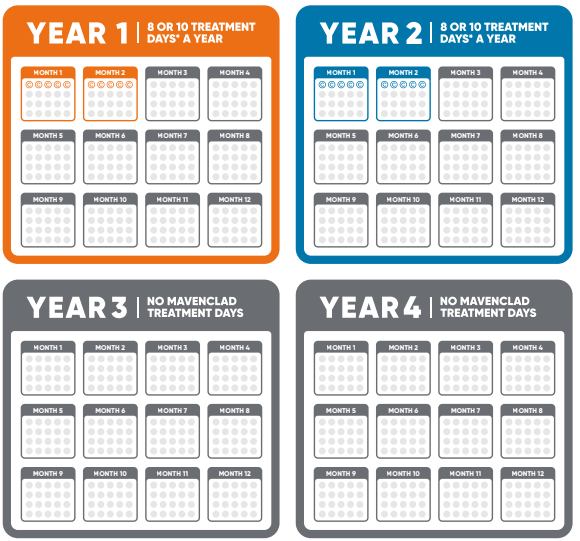
- **First cycle (month 1):** Start any time
- **Second cycle (month 2):** Start 23-27 days after the last dose

Year 2 treatment course:

- **First cycle (month 1):** Start at least 43 weeks after the last dose of the first course/second cycle
- **Second cycle (month 2):** Start 23-27 days after the last dose

Each treatment cycle consists of 4 or 5 consecutive days[1]

Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days. Do not administer more than 2 tablets daily.



Screening and monitoring should be performed before, during, and after treatment. For monitoring recommendations, see pages 6-7.

*1 or 2 pills a day depending on weight.

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MAVENCLAD dosing is based on patient weight[1]

The distribution of the number of tablets across the 2 treatment cycles is provided below. The dosing schedule is the same for both treatment courses (years 1 and 2), although the number of pills per treatment cycle may vary. Patients in the ≈88- to <110-lb (40- to <50-kg) weight range have only 4 days of treatment per treatment cycle, while all other weight ranges have 5 days.

NUMBER OF 10 MG TABLETS PER CYCLE

	TREATMENT WEEK 1 – YEARS 1 & 2						TREATMENT WEEK 2 – YEARS 1 & 2					
WEIGHT RANGE, ≈lb (kg)	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	TOTAL # OF TABLETS IN FIRST CYCLE	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	TOTAL # OF TABLETS IN SECOND CYCLE
88† to <110 (40† to <50 kg)	●	●	●	●	–	4 (40 mg)	●	●	●	●	–	4 (40 mg)
110 to <132 (50 to <60 kg)	●	●	●	●	●	5 (50 mg)	●	●	●	●	●	5 (50 mg)
132 to <154 (60 to <70 kg)	●●	●	●	●	●	6 (60 mg)	●●	●	●	●	●	6 (60 mg)
154 to <176 (70 to <80 kg)	●●	●●	●	●	●	7 (70 mg)	●●	●●	●	●	●	7 (70 mg)
176 to <198 (80 to <90 kg)	●●	●●	●●	●	●	8 (80 mg)	●●	●●	●	●	●	7 (70 mg)
198 to <220 (90 to <100 kg)	●●	●●	●●	●●	●	9 (90 mg)	●●	●●	●●	●	●	8 (80 mg)
220 to <242 (100 to <110 kg)	●●	●●	●●	●●	●●	10 (100 mg)	●●	●●	●●	●●	●	9 (90 mg)
≥242 (≥110 kg)	●●	●●	●●	●●	●●	10 (100 mg)	●●	●●	●●	●●	●●	10 (100 mg)

○ = 1 tablet
○○ = 2 tablets

†The use of MAVENCLAD in patients weighing <88 lb (<40 kg) has not been investigated. Weight ranges in pounds are calculated from kilogram values and have been rounded to the nearest whole number.

Following the administration of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. Treatment during these 2 years may further increase the risk of malignancy. The safety and efficacy of reinitiating MAVENCLAD more than 2 years after completing 2 treatment courses has not been studied.

IMPORTANT SAFETY INFORMATION

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.

PACKAGING DESIGNED FOR PATIENT CONVENIENCE[1]

Patients are dispensed a 1-week supply of MAVENCLAD 10 mg tablets for **each treatment cycle with individualized day packs based on weight**. Each day pack is filled with 1 or 2 tablets and labeled according to the day that the patient should take them. Packaging will vary based on patient weight and is differentiated by color for safety. MAVENCLAD is a cytotoxic drug. Follow applicable special handling procedures.[1]

One-week supply of individualized day packs

Patients take 1 or 2 MAVENCLAD tablets each treatment day:

- Orally, with water, with or without food, and swallowed whole without chewing
- Separate administration of MAVENCLAD and any other oral drugs by at least 3 hours during the 4- to 5-day MAVENCLAD treatment cycles

ONE-WEEK SUPPLY OF INDIVIDUALIZED DAY PACKS FOR A 165-LB (75-KG) PATIENT

Day 1	MAVENCLAD® (cladribine) tablets 10 mg	2 Tablets
Day 2	MAVENCLAD® (cladribine) tablets 10 mg	2 Tablets
Day 3	MAVENCLAD® (cladribine) tablets 10 mg	1 Tablet
Day 4	MAVENCLAD® (cladribine) tablets 10 mg	1 Tablet
Day 5	MAVENCLAD® (cladribine) tablets 10 mg	1 Tablet

For illustrative purposes only. MAVENCLAD dosage will vary based on patient weight.

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Missed dose

If a dose is missed, patients should not take double or extra doses.

- If a dose is not taken on the scheduled day, then the patient must take the missed dose on the following day and extend the number of days in that treatment cycle
- If 2 consecutive doses are missed, the treatment cycle is extended by 2 days

Storage and handling

MAVENCLAD tablets, 10 mg, are white, round, biconvex, and engraved with a "C" on one side and "10" on the other side. Store at controlled room temperature, 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C). Store in original package in order to protect from moisture.

Instruct patients that MAVENCLAD is a cytotoxic drug and to use care when handling MAVENCLAD tablets. Limit direct skin contact with the tablets and wash exposed areas thoroughly. Advise patients to keep the tablets in the original child-resistant blister packaging until just prior to each scheduled dose and consult their pharmacist on the proper disposal of unused tablets.

IMPORTANT SAFETY INFORMATION

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.

Assessments prior to starting each treatment course[1]

Conduct standard cancer screening*:

Follow age-appropriate screening, such as the American Cancer Society (ACS) guidelines, because of the risk of malignancies.† MAVENCLAD is contraindicated in patients with current malignancy[1]

Exclude Pregnancy*:

Exclude pregnancy prior to treatment with MAVENCLAD in females of reproductive potential. MAVENCLAD is contraindicated in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course

Obtain a complete blood count (CBC)*:

Obtain a CBC with differential including lymphocyte count. Lymphocytes must be:

- within normal limits before initiating the first treatment course
- at least 800 cells/µL before initiating the second treatment course

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

Rule out latent or active infections*:

Delay MAVENCLAD treatment until infection is fully resolved or controlled

- **Obtain a baseline (within 3 months) MRI prior to the first treatment course because of the risk of PML (progressive multifocal leukoencephalopathy)**
- **Screen for tuberculosis:** Delay treatment with MAVENCLAD until tuberculosis has been adequately treated
- **Screen for hepatitis B and C:** MAVENCLAD is contraindicated in patients with active chronic infections
- **Exclude HIV infection:** MAVENCLAD is contraindicated in patients with HIV

Confirm vaccinations and immunizations*:

- Vaccination of patients who are seropositive to VZV is recommended with zoster vaccine recombinant, adjuvanted. Patients may be administered zoster vaccine recombinant, adjuvanted at any time prior to or during the year 1 or year 2 course of MAVENCLAD treatment. These patients may also be administered the vaccine if their lymphocyte counts are ≤500 cells/µL
- 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 because of a risk of active vaccine infection.[1]**
- **Vaccination can be considered until 4-6 weeks prior to starting each MAVENCLAD course only if white blood cell counts are within normal limits.** Avoid vaccination with live-attenuated or live vaccines during and after MAVENCLAD treatment while the patient's white blood cell counts are not within normal limits

*Before each treatment course.
†The American Cancer Society recommends that everyone, especially people with chronic illness, have the appropriate cancer screening testing.

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

Assessments prior to starting <u>each treatment cycle</u> within each treatment course

Obtain liver function tests[1]:

- Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to each treatment cycle and course
- Discontinue if clinically significant injury is suspected
- MAVENCLAD is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh score greater than 6)

Ongoing monitoring

Follow standard cancer screening guidelines

Obtain CBCs at 2 and 6 months after start of treatment:

If the lymphocyte count at month 2 is below 200 cells/µL, monitor monthly until month 6. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Patients with lymphocyte counts below 500 cells per microliter should be monitored for signs and symptoms suggestive of infections, including herpes infections

Additional considerations

- 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
- Females of reproductive potential should prevent pregnancy by use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course
  - Because of the risk of fetal harm, do not take MAVENCLAD if you are pregnant or of childbearing potential. Both men and women should use effective birth control while taking MAVENCLAD
- MAVENCLAD is contraindicated in women intending to breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose
- Initiation of MAVENCLAD in patients currently receiving immunosuppressive or myelosuppressive therapy is not recommended

Refer to the full Prescribing Information, located in the pocket, for a complete list of treatment considerations prior to starting each MAVENCLAD treatment course. This page is intended to serve as a summary of that information.

IMPORTANT SAFETY INFORMATION (continued)

- **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.
- **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.

- **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 MAVENCLAD if clinically significant liver 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**.

Please see FULL PRESCRIBING INFORMATION, including **BOXED WARNING**.

References

1. MAVENCLAD [prescribing information]. Rockland, MA: EMD Serono, Inc; 2024.
2. 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.
3. Data on file. Merck KGaA, Darmstadt, Germany.
4. Data on file. Patient years. 2023.
5. Data on file. Marketing status.
6. 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.
7. Giovannoni G, Sorensen PS, Cook S, et al. Efficacy of cladribine tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: a post hoc analysis of the CLARITY study. *Mult Scler.* 2019;25(6)(suppl):819-827. doi:10.1177/1352458518771875

MAVENCLAD IS THE FIRST AND ONLY SHORT-COURSE ORAL RMS THERAPY APPROVED IN THE US[1,3]

130,000+ RMS PATIENTS treated with MAVENCLAD in **90 COUNTRIES** worldwide[8,9]

20+ YEARS of clinical, observational, and real-world experience in MS, resulting in a well-characterized safety profile[1,3]

ZERO CONFIRMED CASES OF PML have been reported in up to 8 years of safety follow-up with patients with MS treated with MAVENCLAD[1]

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

MAVENCLAD DOES NOT CONTINUOUSLY SUPPRESS THE IMMUNE SYSTEM[1,10,11]

MAVENCLAD is associated with a reduction,* and subsequent recovery, in lymphocyte count. At the end of the second treatment course, 2% of clinical study patients had lymphocyte counts less than 500 cells/µL; median time to recovery to at least 800 cells/µL was approximately 28 weeks.[1]

UP TO 10 DOSING DAYS PER YEAR

MAVENCLAD is administered in 2 treatment courses, approximately 1 year apart for 2 years. Each course is taken over 2 weeks. Each week of treatment includes 4 to 5 days of daily dosing, approximately 1 month apart for 2 months. Dosing depends on weight.[1]

Screening and monitoring should be performed before, during, and after treatment.

*Pooled data from CLARITY, CLARITY Extension, and PREMIERE. CLARITY: CLAdRIbine Tablets treating multiple sclerosis orallY; PML: progressive multifocal leukoencephalopathy; RMS: relapsing multiple sclerosis; µL: microliter.

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