MAVENCLAD®
(cladribine) tablets 10 mg

Only MAVENCLAD can deliver proven efficacy in RRMS and SPMS with a maximum of 20 days of oral treatment over 2 years.[1,2]

RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis.

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.

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EMD SERONO

MAVENCLAD WAS STUDIED IN A 2-YEAR PIVOTAL PHASE III TRIAL[1]

Phase III CLARITY study design[2]

CLARITY was a Phase III, multicenter, randomized, double-blind trial of MAVENCLAD versus placebo in patients with relapsing-remitting multiple sclerosis (RRMS). Patients were eligible if they met certain criteria, including at least 1 MS relapse within the past 12 months, EDSS scores ≤5.5, and <2 prior DMT failures 1,184 patients completed the study at 2 years (96 weeks). Endpoints at 2 years included:

Primary endpoint[2]: Annualized relapse rate

Key secondary endpoints[2]: Proportion of relapse-free patients; Time to 3-month confirmed disability progression; Mean number of T1-Gd+ and new or enlarging T2 lesions; Mean number of combined unique MRI lesions

In the trial, 74% of patients taking MAVENCLAD 3.5 mg/kg were treatment-naive for drugs used to treat relapsing forms of MS.

Proven efficacy

In the pivotal Phase III, randomized, placebo-controlled CLARITY trial, MAVENCLAD demonstrated[1]:

ARR

RELATIVE REDUCTION IN ARR AT 2 YEARS

↓58% VS PLACEBO
P<0.001

0.14	vs	0.33
MAVENCLAD (n=433)		placebo (n=437)[1]

EDSS

REDUCTION IN RISK OF 3-MONTH CONFIRMED EDSS PROGRESSION

↓33% VS PLACEBO
P=0.02

(n=433)	vs	(n=437)
MAVENCLAD		placebo

HR=0.67; 95% CI, 0.48 to 0.93

T1-Gd+

RELATIVE REDUCTION IN MEAN NUMBER OF T1-Gd+ LESIONS

↓90% VS PLACEBO
P<0.001

0.09	vs	0.86
MAVENCLAD (n=433) SD=0.30		placebo (n=437) SD=1.78[1]

T2-weighted

RELATIVE REDUCTION IN MEAN NUMBER OF NEW OR ENLARGING T2-WEIGHTED LESIONS

↓75% VS PLACEBO
P<0.001

0.35	vs	1.38
MAVENCLAD (n=433) SD=0.66		placebo (n=437) SD=2.11[1]

81% of patients were **relapse free** for 2 years vs 63% on placebo (95% CI: 75.7, 83.6; 56.1, 65.6).[1]

XX% of patients taking MAVENCLAD 3.5mg/kg had **zero new T1-Gd+ lesions** (median MAVENCLAD 0, placebo 0.33, range 0-4.33)

XX% of patients taking MAVENCLAD 3.5mg/kg had **zero new or enlarging T2-weighted lesions** (median MAVENCLAD 0, placebo 0.67, range 0-4.33)

SELECT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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.

In the Phase III trial, significantly more patients achieved no evidence of disease activity (NEDA) vs placebo[4]

44% MAVENCLAD (n=402) vs **16%** placebo (n=379) **NEDA**

NEDA POST HOC ANALYSIS (OVERALL POPULATION):

RELAPSE FREE: 80% MAVENCLAD (n=409) vs **60%** placebo (n=401)

3-MONTH EDSS PROGRESSION FREE: 86% MAVENCLAD (n=407) vs **79%** placebo (n=388)

T1-GD+ LESION FREE: 87% MAVENCLAD (n=422) vs **47%** placebo (n=424)

NEW OR ENLARGING T2 LESION FREE: 62% MAVENCLAD (n=422) vs **28%** placebo (n=424).

NEDA was evaluated in a post hoc analysis of data from the CLARITY study and defined as relapse free, no 6-month sustained, no change in EDSS score, no new T1-Gd+ lesions, and no new or enlarging T2 lesions. Of the 1,326 patients in the CLARITY study, 1,192 were assessable for NEDA at 96 weeks. MRI scans were obtained at the prestudy evaluation and at 24, 48, and 96 weeks. 47% of people taking MAVENCLAD had no evidence of disease activity compared with 17% with placebo (OR [95% CI]: 4.25 [3.03-5.96]).[4]

Efficacy in active SPMS: a post-hoc subgroup analysis of clarity

In a post-hoc analysis of the subgroups in the CLARITY study, 174 (**40%**) of patients in the placebo arm and 161 (**37%**) of patients in the MAVENCLAD 3.5 mg/kg arm were identified as having baseline EDSS ≥3.5, which can serve as a proxy of active secondary progressive MS in relapsing patients. In a second post hoc analysis of the CLARITY, NEDA was evaluated in patients across subgroups, including the baseline EDSS ≥3.5 patient subgroup.

In this **baseline EDSS ≥3.5** patient subgroup, MAVENCLAD demonstrated:

57% relative **reduction in ARR** versus placebo (MAVENCLAD: 0.15 vs placebo: 0.35; P <0.001)

49% **NEDA** in the MAVENCLAD arm versus 17% of patients in the placebo arm (OR: 4.51, P <0.0001)

ARR: annualized relapse rate; CI: confidence interval; CLARITY: CLAdRIbine Tablets treating multiple sclerosis orallY; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; HR: hazard ratio; OR: odds ratio; SD: standard deviation; T1-Gd+: T1 gadolinium-enhanced.

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.

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MAVENCLAD® (cladribine) tablets 10 mg

WELL-CHARACTERIZED SAFETY AND TOLERABILITY PROFILE

ADVERSE REACTIONS ≥ 5% FOR MAVENCLAD AND HIGHER THAN PLACEBO

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

DISCONTINUATION RATE DUE TO ADVERSE REACTIONS

In the pivotal trial, **3.5%** of patients receiving MAVENCLAD discontinued treatment due to adverse reactions vs **2.1%** of patients receiving placebo.[2]

TRIAL COMPLETION

92% percent of patients treated with MAVENCLAD completed the full 96 weeks of the study vs **87%** of patients receiving placebo.

In up to 8 years of safety registry follow-up:

- **No case of PML has been reported in MS[1‡]**
  In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported in the postmarketing setting
- **No increased risk of secondary autoimmune disease vs placebo[1, 5-7]**

Other reported ARs

Hypersensitivity: In clinical studies, 11% of patients on MAVENCLAD had hypersensitivity adverse reactions, compared to 7% on placebo.

Alopecia: Alopecia occurred in 3% of patients on MAVENCLAD compared to 1% on placebo.

Herpes Meningoencephalitis: Fatal herpes meningoencephalitis occurred in one patient on MAVENCLAD, at a higher dosage and longer duration of therapy than the approved MAVENCLAD dosage and in combination with interferon beta-1a treatment.

Seizures: In clinical studies, serious events of seizure occurred in 0.3% of patients on MAVENCLAD compared to 0% on placebo. Serious events included generalized tonic-clonic seizures and status epilepticus. It is unknown whether these events were related to the effects of multiple sclerosis alone, to MAVENCLAD, or to a combination of both.

‡Through March 29, 2019.

Lymphopenia[1]

In clinical studies, 87% of MAVENCLAD 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.

Mostly mild to moderate lymphopenia (2% of patients had lymphocyte counts less than 500 cells/mm^3)

26% of patients treated with **MAVENCLAD** had nadir absolute lymphocyte counts less than 500 cells/mm^3

1% of patients treated with **MAVENCLAD** had nadir absolute lymphocyte counts <200 cells/mm^3

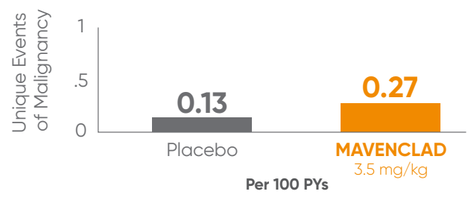
Lymphocytes must be within normal limits before initiating the first treatment course, and at least 800 cells/mm^3 before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells/mm^3. If this recovery takes more than 6 months, the patient should not receive further treatment with MAVENCLAD.

Malignancy[1]

In controlled and extension clinical studies worldwide, malignancies occurred more frequently with MAVENCLAD [10 events in 3,754 PYs] compared with placebo [3 events in 2,275 PYs]

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.

Malignancy rates compared to placebo[1]



Pregnancy

There is no adequate data on the developmental risk associated with the use of MAVENCLAD in pregnant women, therefore it is contraindicated in pregnant women who do not plan to use effective contraception. Advise women of the potential fetal risk during MAVENCLAD dosing and for 6 months after the last dose.

Infections[1]

Infections occurred in 49% of patients on MAVENCLAD compared to 44% on placebo. The most frequent serious infections in MAVENCLAD patients included herpes zoster and pyelonephritis.

- HIV infection, active tuberculosis, and active hepatitis must be excluded before initiating MAVENCLAD
- Patients should also be screened for latent infections, particularly tuberculosis and hepatitis B and C, before treatment initiation in both treatment years
- Tuberculosis developed in 3 out of 1,976 (0.2%) patients on MAVENCLAD. All 3 cases occurred in regions where tuberculosis is endemic. One case of tuberculosis was fatal, and 2 cases resolved with treatment.
- 6% of patients on MAVENCLAD developed a herpes viral infection compared to 2% on placebo.
- Patients who are antibody-negative to varicella zoster virus should be vaccinated prior to treatment. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD.

PY: patient-year.

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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. 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.

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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.

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 full Prescribing Information, including boxed WARNING for additional information.

Learn more about this short-course oral therapy for multiple sclerosis at MAVENCLAD.com/hcp

REFERENCES:

1. MAVENCLAD [prescribing information]. Rockland, MA: EMD Serono, Inc; 2019. **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. CLARITY post hoc efficacy analysis (2018). **4.** Giovannoni G, Cook S, Rammohan K, et al; for the CLARITY Study Group. Sustained disease-activity-free status in patients with relapsing remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. *Lancet Neurol*. 2011;10(4):329-337. **5.** Giovannoni G, Soelberg Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: results from the randomized extension trial of the CLARITY study. *Mult Scler*. 2018;24(12):1594-1604. **6.** Cook S, Vermersch P, Comi G, et al; for the CLARITY Study Group. Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablet treating multiple sclerosis orallY) study. *Mult Scler*. 2011;17(5):578-593. **7.** Cook S, Leist T, Comi G, et al. Safety of cladribine tablets in the treatment of patients with multiple sclerosis (MS): an integrated analysis from the MS clinical development program [abstract EP1141]. *Eur J Neurol*. 2017;24(suppl1):194-195.

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