Drug Monograph

Drug/Drug Class:	**Mavenclad® (cladribine) oral tablets / Multiple Sclerosis Agents**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each tablet of Mavenclad contains 10 mg of cladribine.. Distributed by: EMD Serono, Inc. Rockland, MA 02370
Summary of Findings:	The efficacy of Mavenclad in patients with relapsing forms of Multiple Sclerosis (MS) was assessed in a 96-week randomized, double-blind, placebo-controlled clinical study. Mavenclad 3.5 mg per kg significantly lowered the annualized relapse rate, reduced the proportion of patients with confirmed disability progression, reduced the time to first qualifying relapse, and displayed a lower mean number of MRI T1 Gadolinium-enhancing lesions and new or enlarging MRI T2 hyperintense lesions.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Non-Preferred Agent ☐ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2,3,4]

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory, demyelinating disease of the central nervous system that disrupts communication between the brain and other parts of the body. MS has an unpredictable clinical course during which time neurologic disability accumulates. MS is categorized into clinical subtypes: Clinically isolated syndrome (the first attack of MS), Relapsing-remitting MS (RRMS), Secondary progressive MS (SPMS), and Primary Progressive MS (PPMS). Most people are diagnoses between 20 to 50 years old with RRMS being the most common form at diagnosis. Disease progression is determined by MRI evidence of contrast enhancing lesions and/or new or enlarging T2 lesions; or clinical relapses.

SPMS is the largest category of MS and develops in approximately 80% of patients with RRMS over time, resulting in the greatest amount of neurologic disability. The average person in the United States has about a 1 in 750 chance of developing MS with MS being two to three times more common in women than men.

Dosage Form(s) [1]

Mavenclad is available as 10 mg tablets of cladribine.

Manufacturer [1]

Distributed by: EMD Serono, Inc. Rockland, MA 02370

Indication(s) [1]

Mavenclad is a purine antimetabolite 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.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

The mechanism by which Mavenclad exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes.

Pharmacokinetics:

	Mavenclad®
Absorption	Bioavailability of Mavenclad is approximately 40%.
Distribution	Intracellular concentrations of Mavenclad and/or its metabolites in human lymphocytes were approximately 30 to 40 times extracellular, in vitro, has the potential to penetrate the blood brain barrier.
Volume of Distribution	480 to 490 liters
Protein Binding	20% and is independent of concentration, in vitro
Metabolism	Mavenclad is a prodrug that is phosphorylated to Cd-AMP by deoxycytidine kinase (and also by deoxyguanosine kinase in the mitochondria) in lymphocytes. Cd-AMP is further phosphorylated to cladribine diphosphate (Cd-ADP) and the active moiety Cd-ATP. The dephosphorylation and deactivation of Cd-AMP is catalyzed by cytoplasmic 5'-nucleotidase (5'-NTase).
Elimination	After administration of 10 mg oral Mavenclad in MS patients, 28.5 percent of the dose was excreted unchanged via the renal route. Renal clearance exceeded the glomerular filtration rate, indicating active renal secretion, estimated median apparent renal clearance is 22.2 liter per hour and non-renal clearance is 23.4 liter per hour
Half-life	Terminal half-life is approximately 1-day

CLARITY - Efficacy of Mavenclad® in patients with relapsing forms of MS

STUDY DESIGN	96-week randomized, double-blind, placebo-controlled clinical study in patients with relapsing forms of MS
INCLUSION CRITERIA	At least 1 relapse in the previous 12 months, age 18 to 65
EXCLUSION CRITERIA	Patients not meeting inclusion criteria.
TREATMENT REGIMEN	1,326 patients were randomized to receive either placebo (n = 437), or a cumulative oral dosage of Mavenclad 3.5 mg per kg (n = 433) or 5.25 mg per kg body weight (n = 456) over the 96-week study period in 2 treatment courses. Patients randomized to the 3.5 mg per kg cumulative dose received a first treatment course at Weeks 1 and 5 of the first year and a second treatment course at Weeks 1 and 5 of the second year. Patients randomized to the 5.25 mg per kg cumulative dose received additional treatment at Weeks 9 and 13 of the first year. The primary outcome of Study 1 was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients with confirmed disability progression, the time to first qualifying relapse, the mean number of MRI T1 Gadolinium-enhancing (Gd+) lesions, and new or enlarging MRI T2 hyperintense lesions. Disability progression was

	measured in terms of a 3-month sustained change in EDSS score of at least one point, if baseline EDSS score was between 0.5 and 4.5 inclusively, or at least 1.5 points if the baseline EDSS score was 0, or at least 0.5 point if the baseline EDSS score was at least 5, over a period of at least 3 months.
RESULTS	Ninety-two percent of patients treated with Mavenclad 3.5 mg per kg and 87% of patients receiving placebo completed the full 96 weeks of the study. Higher cumulative doses did not add any clinically meaningful benefit, but were associated with a higher incidence in grade 3 lymphopenia or higher (44.9% in the 5.25 mg per kg group vs. 25.6% in the 3.5 mg per kg group). Mavenclad 3.5 mg per kg significantly lowered the annualized relapse rate. The relative reduction in ARR was 58% in the Mavenclad 3.5 mg/kg group. 81% of patients receiving Mavenclad 3.5 mg/kg did not experience a relapse, compared to 63% of patients receiving placebo. 13% of patients receiving Mavenclad had 3 month EDSS progression compared to 19% of patients receiving placebo.
SAFETY	Not specified.

Contraindications [(1)]

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during Mavenclad dosing and for 6 months after the last dose in each treatment course.
- HIV infection.
- Active chronic infections (e.g., hepatitis or tuberculosis).
- 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 [(1)]

- **Black boxed Warnings:**
  - **Malignancies: Mavenclad may increase the risk of malignancy. Mavenclad is contraindicated in patients with current malignancy; evaluate the benefits and risks on an individual basis for patients with prior or increased risk of malignancy.**
  - **Risk of Teratogenicity: 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 risk of fetal harm.**
- Lymphopenia: Monitor lymphocyte counts before, during and after treatment.
- Infections: Screen patients for latent infections; consider delaying treatment until

infection is fully controlled. Vaccinate patients who are 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.

- Hematologic toxicity: Monitor complete blood count before, during and after treatment.
- Graft-versus-host-disease with blood transfusion: Irradiation of cellular blood components is recommended.
- Liver injury: Obtain tests prior to treatment. Discontinue if clinically significant injury is suspected.

Adverse Effects [1]

Adverse Effects ≥3%	**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

Drug Interactions [1]

- Immunosuppressive drugs: Consider overlapping effects on immune system, when used sequentially. Concomitant use not recommended.
- Hematotoxic drugs: Monitor patients for additive effects on the hematological profile.
- Antiviral and antiretroviral drugs: Avoid concomitant use.
- BCRP or ENT/CNT inhibitors: May alter bioavailability of cladribine. Avoid concomitant use.

Dosage and Administration [1]

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

Dose Table

Weight Range	Dose in mg per Cycle	
kg	First Cycle	Second Cycle
40* to less than 50	40 mg	40 mg
50 to less than 60	50 mg	50 mg
60 to less than 70	60 mg	60 mg
70 to less than 80	70 mg	70 mg
80 to less than 90	80 mg	70 mg
90 to less than 100	90 mg	80 mg
100 to less than 110	100 mg	90 mg
110 and above	100 mg	100 mg

* The use of Mavenclad in patients weighing less than 40 kg has not been investigated

Administration of First Treatment Course

• First Course/First Cycle: start any time.

• First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle.

Administration of Second Treatment Course

• Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle.

• Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle.

- 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.
- 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.
- 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 two consecutive doses are missed, the treatment cycle is extended by 2 days.
- Mavenclad tablets are taken orally, with water, swallowed whole without chewing, and taken with or without food.
- Separate administration of Mavenclad and any other oral drugs by at least 3 hours during the 4 to 5 day of treatment cycles.
- Mavenclad is a cytotoxic drug. Follow applicable special handling and disposal procedure. Mavenclad is an uncoated tablet and must be swallowed immediately once removed from the blister. If a tablet is left on a surface, or if a broken or fragmented tablet is released from the blister, the area must be thoroughly washed with water.
- The patient's hands must be dry when handling the tablets and washed thoroughly

afterwards. Avoid prolonged contact with skin.

Cost [1]

BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ TREATMENT*
Mavenclad	EMD Serono	10 mg tablet	40 mg	$111,914 per lifetime
			50 mg	$139,888 per lifetime
			60 mg	$167,862 per lifetime
			70 mg	$195,835 per lifetime
			80 mg	$223,809 per lifetime
			90 mg	$251,783 per lifetime
			100 mg	$279,756 per lifetime
Mayzent	Novartis	2 mg tablet	2 mg daily	$86,124 per year

*Maximum Allowable Cost

Conclusion [1,2]

Mavenclad is approved for the treatment of adults with relapsing-remitting multiple sclerosis and active secondary progressive disease. Due to safety concerns, Mavenclad is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternative drug indicated for the treatment of MS. Mavenclad was first reviewed and rejected by the FDA in 2011, in part due to concerns that it had higher cancer risk. Since then, additional studies and analysis of cancer risk compared to other disease-modifying drugs in eleven trials found no evidence for increased risk of cancer in patients taking Mavenclad compared to other therapies. Mavenclad still carries a black box warning to account for possible increased risk of malignancy as well as risk of fetal harm. The efficacy of Mavenclad was shown in a clinical trial called CLARITY which studied 1,326 patients with relapsing forms of MS who had at least one relapse in the previous 12 months. Mavenclad 3.5 mg/kg results in a 58% relative reduction in annualized relapse rate over placebo, with 81% of patients having no relapses compared to 63% of patients receiving placebo. Mavenclad is available as 10 mg tablet with a unique dosing regimen of two treatment courses for 4-5 days for year one and again for year two. No drug is give in years 3 or 4, although the drug remains active during this time.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List as non-preferred

References

1) Product Information: Mavenclad® EMD Serono, Inc. Rockland, MA 02370 1993.
2) IPD Analytics Rx Insights_New Drug Approval Review_Mavenclad_04 2019.pdf
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4) Olek, Michael; Mowry, Ellen. Treatment of progressive multiple sclerosis in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on July 4, 2019.)

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