Clinical Policy Title:	cladribine
Policy Number:	RxA.213
Drug(s) Applied:	Mavenclad®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Cladribine (Mavenclad®) is a cytotoxic purine antimetabolite. It 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.

Limitation(s) of use: Mavenclad® is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
cladribine (Mavenclad®)	relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (SPMS)	• 3.5 mg/kg divided into 2 yearly treatment courses. Each treatment course (1.75mg/kg) divided into 2 treatment cycles. • Divide the 1.75 mg/kg dose over 2 cycles, each cycle lasting 4 to 5 consecutive days; do not administer more than 20 mg/day. • In the first-year treatment course, initiate the first cycle at any time; administer the second cycle 23 to	2 tablets/day, 10 tablets/cycle, 2 cycles/course/year, 2 courses total

Drug Name	Indication	Dosing Regimen	Maximum Dose
		27 days after the last dose of the first cycle. • In the second-year treatment course, initiate the first cycle ≥43 weeks after the last dose of the first year's second cycle. • Administer the second cycle 23 to 27 days after the last dose of the second year's first cycle. • Following 2 years of treatment, do not administer oral cladribine during the next 2 years. **Courses and cycles** Course one (year one) • First cycle: start any time. • Second cycle: start 23 to 27 days after last dose of first cycle. Course two (year two) • First cycle: start at least 43 weeks after last dose of first course's second cycle. • Second cycle: start 23 to 27 days after the last dose of second course's first cycle.	

Drug Name	Indication	Dosing Regimen	Maximum Dose
		Weight range (kg): # of tablets - first and second cycles • 40* to less than 50 kg 40 mg (4 tablets) (cycles 1 and 2) • 50 to less than 60 kg 50 mg (5 tablets) (cycles 1 and 2) • 60 to less than 70 kg 60 mg (6 tablets) (cycles 1 and 2) • 70 to less than 80 kg 70 mg (7 tablets) (cycles 1 and 2) • 80 to less than 90 kg 80 mg (8 tablets) (cycle 1) 70 mg (7 tablets) (cycle 2) • 90 to less than 100 kg 90 mg (9 tablets) (cycle 1) 80 mg (8 tablets) (cycle 2) • 100 to less than 110 kg o 100 mg (10 tablets) (cycle 1) 90 mg (9 tablets) (cycle 2) • 110 kg and above 100 mg (10 tablets) (cycles 1 and 2) *The use of Mavenclad® in patients weighing less than 40 kg has	

		not been investigated.	

Dosage Forms

- Tablet: 10 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the provisions of the pharmacy benefit administer by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all):

1. Diagnosis of one of the following (a or b):
   a. Relapsing-remitting MS (RRMS),
   b. Secondary progressive MS (SPMS);
2. Trial and failure of at least 2 preferred disease modifying therapies, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced.
   *Prior authorization is required for all disease modifying therapies for MS.
3. Prescribed by or in consultation with a neurologist;
4. Age ≥ 18 years;
5. Mavenclad® is not prescribed concurrently with other disease modifying therapies for MS; *(see Appendix D)*
6. Dose does not exceed any of the following: 2 tablets per day, 10 tablets per cycle, 2 cycles per course, 1 course per year.

Approval Duration
Commercial: 12 months - up to 1 course (2 courses lifetime total)
Medicaid: 12 months - up to 1 course (2 courses lifetime total)

II. Continued Therapy Approval

A. Multiple Sclerosis (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Mavenclad® is not prescribed concurrently with other disease modifying therapies for MS; (*see Appendix D)*
4. Dose does not exceed any of the following: 2 tablets per day, 10 tablets per cycle, 2 cycles per course, 1 course per year.

Approval Duration
Commercial: 12 months - up to 1 course (2 courses lifetime total)
Medicaid: 12 months - up to 1 course (2 courses lifetime total)

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CIS: Clinically Isolated Syndrome
FDA: Food and Drug Administration
MS: Multiple Sclerosis
RRMS: Relapsing-Remitting Multiple Sclerosis
SPMS: Secondary Progressive Multiple Sclerosis

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
Avonex® (interferon beta-1a)	30 mcg IM every week	30 mcg/week
Plegridy® (peginterferon beta-1a)	125 mcg SC 2 weeks	125 mcg/2 weeks
glatiramer acetate (Copaxone®, Glatopa®)	20 mg SC daily or 40 mg SC three times a week	varies
Aubagio®(teriflunomide)	7 mg or 14 mg PO once daily	14 mg/day
Tecfidera® (dimethyl fumarate)	120 mg PO BID for 7 days, followed by 240 mg PO BID	480 mg/day
Mayzent® (siponimod)	All patients: Day 1 and 2: 0.25 mg PO once daily Day 3: 0.5 mg PO once daily, Day 4: 0.75 mg PO once daily CYP2C9 genotypes *1/*1, *1/*2, or *2/*2: Day 5: 1.25 mg PO once daily Day 6 and onward: 2 mg PO once daily CYP2C9 genotypes *1/*3 or *2/*3: Day 5 and onward: 1 mg PO once daily	2 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings
- Contraindication(s):
  - 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.

- Boxed Warning(s):
  - It may increase the risk of malignancy. Mavenclad® is contraindicated in patients with current malignancy.
  - 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.
  - Mavenclad® can cause bone marrow suppression, renal toxicity or neurotoxicity

APPENDIX D: General Information

Disease-modifying therapies for MS include:

- Infusion therapies
  - natalizumab (Tysabri®)
  - mitoxantrone
  - ocrelizumab (Ocrevus™)
  - alemtuzumab (Lemtrada®)
- Injectable therapies
  - glatiramer (Copaxone®, Glatopa®)
  - interferon beta-1a (Avonex®, Rebif®)
  - interferon beta-1b (Betaseron®, Extavia®)
  - peginterferon beta-1a (Plegridy®)
- Oral therapies
  - dimethyl fumarate (Tecfidera®)
  - monomethyl fumarate (Bafiertam™)
  - diroximel fumarate (Vumerity®)
  - teriflunomide (Aubagio®)
  - fingolimod (Gilenya™)
  - siponimod (Mayzent®)
  - ozanimod (Zeposia®)
  - cladribine (Mavenclad®)
  - dalfampridine (Ampyra®)

- Assessments prior to starting each Mavenclad® treatment course:
  - Cancer screening: Follow standard cancer screening guidelines because of the risk of malignancies;
  - Pregnancy: Exclude pregnancy prior to treatment with Mavenclad® in females of reproductive potential;
  - Complete Blood Count (CBC): Obtain a CBC with differential including lymphocyte count. Lymphocytes must be within normal limits before initiating the first treatment course. Lymphocytes must be at least 800 cells per microliter before initiating the second treatment course;
  - Infections:
    - Exclude HIV infection.
    - Perform tuberculosis screening.
    - Screen for hepatitis B and C.
    - Evaluate for acute infection. Consider a delay in Mavenclad® treatment until any acute infection is fully controlled.
    - Vaccination of patients who are antibody-negative for varicella zoster virus is recommended prior to initiation of Mavenclad®.
    - Administer all immunizations according to immunization guidelines prior to starting Mavenclad®. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting Mavenclad®.

- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).
- Liver injury: Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels.

References

1. Mavenclad® Prescribing Information. Rockland, MD: EMD Serono, Inc.; April 2019. Available at: https://www.mavenclad.com. Accessed March 16, 2021.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: https://www.clinicalkey.com/pharmacology/. Accessed March 16, 2021.
3. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology, 2018;90:777-788. doi:10.1212/WNL.0000000000005347.
4. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology, 2018;90:789-800. doi:10.1212/WNL.0000000000005345.
5. Costello K, Kalb R. The use of disease-modifying therapies in multiple sclerosis, principles and current evidence – a consensus paper by the Multiple Sclerosis Coalition. Revised September 2019. Available at http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c- 4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed March 16, 2021.
6. Mavenclad® Prescribing Information.EMD Serono, Inc., March 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022561s000lbl.pdf. Accessed March 16, 2021.
7. Mavenclad® Lexicomp [database online]. Available at https://online.lexi.com/lco/action/home. Accessed March 16, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title description updated. 2. Initial Approval criteria updated to: Trial and failure of at least 2 preferred disease modifying therapies, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced. 3. Continuation therapy criteria II.A.1. updated to "Member is currently receiving medication that has been authorized by RxAdvance or the	07/12/2020	09/14/2020

member has met initial approval criteria listed in this policy” 4. Initial therapy and continued therapy approval duration was updated to include commercial and Medicaid. 5. Appendix B, therapeutic alternatives, dosing regimen was updated. 6. Appendix C, contraindications/boxed warnings was updated. 7. Appendix D, general information was updated with information on assessments to be done prior to starting each Mavenclad® treatment course. 8. References were updated.		
Policy was reviewed: 1. Policy title was updated. 2. Dosing regimen was updated. 3. Continued therapy criteria II.A.1 was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance..” 4. APPENDIX B was updated: Included therapeutic alternatives Aubagio®, Tecfidera®, Mayzent® ; 5. References were reviewed and updated.	3/16/2021	6/10/2021