RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	dimethyl fumarate
Policy Number:	RxA.505
Drug(s) Applied:	Tecfidera®
Original Policy Date:	01/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Dimethyl fumarate (Tecfidera®) is a nuclear factor-like 2 activator. It is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
dimethyl fumarate (Tecfidera®)	Relapsing MS	Starting: 120 mg PO BID for 7 days Maintenance: 240 mg PO BID	480 mg/day

Dosage Forms

- Delayed-release capsules: 120 mg, 240 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.

I. Initial Approval Criteria

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

1. Diagnosis of one of the following (a, b, or c):
   a) Clinically isolated syndrome;
   b) Relapsing-remitting Multiple Sclerosis ;
   c) Secondary progressive Multiple Sclerosis ;
2. Trial and failure of at least two (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 Multiple Sclerosis.
3. Age 18 years of age or older;
4. Prescribed by or in consultation with a neurologist;
5. Dimethyl fumarate is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix B*);

6. Dose does not exceed:
    a. Starting dose: 240 mg (2 capsules) per day for 7 days;
    b. Maintenance dose: 480 mg (2 capsules) per day.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving the 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 (i.e. reduction in the number of acute attacks, no new brain lesions, disease stabilization);
3. Dimethyl fumarate is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix B*);
4. If request is for a dose increase, new dose does not exceed 480 mg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
IM: Intramuscular/intramuscularly
IV: Intravenous/intravenously
MS: Multiple Sclerosis
PO: By mouth
SC: Subcutaneous/subcutaneously

APPENDIX B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Infusion Therapies		
natalizumab (Tysabri®)	300 mg IV every 4 weeks	300 mg/4 weeks
mitoxantrone	12 mg/m^2 given as a short (approximately 5 to 15 minutes) IV infusion every 3 months	Cumulative lifetime dose of ≥ 140 mg/m^2
ocrelizumab (Ocrevus™)	Initial 300 mg IV infusion with a second 300 mg IV infusion two weeks later, followed by subsequent doses of 600 mg via IV infusion every 6 months	600 mg/6 months
alemtuzumab (Lemtrada®)	IV infusion for 2 or more treatment courses:	See regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• First course: 12 mg/day on 5 consecutive days • Second course: 12 mg/day on 3 consecutive days 12 months after first course • Subsequent courses as needed: 12 mg/day on 3 consecutive days 12 months after any prior course	
Injectable therapies		
glatiramer (Copaxone®, Glatopa®)	20 mg SC once daily or 40 mg SC three times weekly	20 mg/day or 40 mg three times per week
interferon beta-1a (Avonex®, Rebif®)	Avonex®: 30 mcg IM weekly Rebif®: 22 mcg or 44 mcg SC three times weekly	Avonex®: 30 mcg/week Rebif®: 44 mcg three times per week
interferon beta-1b (Betaseron®, Extavia®)	250 mcg SC every other day	250 mg every other day
peginterferon beta-1a (Plegridy®)	125 mcg SC every 2 weeks	125 mcg/2 weeks
Oral therapies		
monomethyl fumarate (Bafiertam™)	Initial: 95 mg PO twice daily; after 7 days, increase to the maintenance dose of 190 mg PO twice daily.	380mg/day
diroximel fumarate (Vumerity®)	Starting: 231 mg PO twice daily for 7 days Maintenance: 462 mg PO twice daily	924 mg/day
teriflunomide (Aubagio®)	7 mg or 14 mg PO daily	14 mg/day
fingolimod (Gilenya™)	0.5 mg PO daily	0.5 mg/day
siponimod (Mayzent®)	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 For CYP2C9 genotypes *1/*1, *1/*2, or *2/*2: Day 5: 1.25 mg PO once daily Day 6 & onward: 2 mg PO once daily For CYP2C9 genotypes *1/*3 or *2/*3: Day 5 & onward: 1 mg PO once daily	2 mg/day
ozanimod (Zeposia®)	Days 1-4: 0.23 mg PO once daily Days 5-7: 0.46 mg PO once daily	0.92 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Day 8 & onward: 0.92 mg PO once daily	
cladribine (Mavenclad®)	3.5 mg/kg over 2-year treatment course, administered as 1.75 mg/kg in each year. Divide the 1.75 mg/kg dose over 2 cycles, each cycle lasting 4 to 5 consecutive days	20mg/day
dalfampridine (Ampyra®)	10 mg PO twice daily (approximately 12 hours apart)	20 mg/day

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to dimethyl fumarate or any of the excipients of Tecfidera

- Boxed Warning(s):
  - None reported

APPENDIX D: General Information

Warnings and Precautions:

- Anaphylaxis and angioedema: Discontinue and do not restart Tecfidera if these occur.
- Progressive multifocal leukoencephalopathy (PML): Withhold Tecfidera at the first sign or symptom suggestive of PML.
- Herpes zoster and other serious opportunistic infections: Consider withholding Tecfidera in cases of serious infection until the infection has resolved.
- Lymphopenia: Obtain a CBC including lymphocyte count before initiating Tecfidera, after 6 months, and every 6 to 12 months thereafter. Consider interruption of Tecfidera if lymphocyte counts $<0.5 \times 10^9$/L persist for more than six months.
- Liver injury: Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiating Tecfidera and during treatment, as clinically indicated. Discontinue Tecfidera if clinically significant liver injury induced by Tecfidera is suspected.

References

1. Tecfidera Prescribing Information. Cambridge, MA: Biogen Inc.; February 2020. Available at http://www.tecfidera.com Accessed September 03, 2020.
2. Costello K, Halper J, Kalb R, Skutnik L, Rapp R. The use of disease-modifying therapies in multiple sclerosis, principles and current evidence – a consensus paper by the Multiple Sclerosis Coalition. March 2017. Accessed September 03, 2020.
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(17): 777-788. Full guideline available at: https://www.aan.com/Guidelines/home/GetGuidelineContent/904. Accessed September 03, 2020.
4. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Accessed September 14, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/01/2020	03/06/2020
Policy updated. 1. Initial approval criteria updated to include – "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." 2. Approval length for commercial line of business from length of benefit to 6 months for initial and 12 months for continuation therapy. 3. Appendix B and D updated.	8/27/2020	9/14/2020
Policy updated. 1. Policy title table updated. 2. Policy was updated to all lines of business 3. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 4. Appendix B updated.	09/14/2020	12/07/2020