Clinical Policy Title:	dimethyl fumarate
Policy Number:	RxA.505
Drug(s) Applied:	Tecfidera®
Original Policy Date:	01/2020
Last Review Date:	09/14/2021
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 orally twice daily for 7 days Maintenance: 240 mg orally twice daily	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 one (1) preferred disease modifying therapy (Avonex®, Betaseron®, Copaxone®, Vumerity®, Bafiertam®, or Kesimpta®), 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. Member had inadequate response to generic dimethyl fumarate;
5. Prescribed by or in consultation with a neurologist;
6. Tecfidera or its generic dimethyl fumarate is not prescribed concurrently with other disease modifying

therapies for MS (see Appendix B);
7. 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
MS: 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	Dose Limit/ Maximum Dose
Infusion Therapies		
natalizumab (Tysabri®)	300 mg intravenously every 4 weeks	300 mg/4 weeks
mitoxantrone	12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months	Cumulative lifetime dose of ≥ 140 mg/m^2
ocrelizumab (Ocrevus™)	Initial 300 mg intravenous infusion with a second 300 mg intravenous infusion two weeks later, followed by subsequent doses of 600 mg via intravenous infusion every 6 months	600 mg/6 months
alemtuzumab (Lemtrada®)	Intravenous infusion for 2 or more treatment courses: • First course: 12 mg/day on 5 consecutive days • Second course: 12 mg/day on 3 consecutive days 12 months after first course	See regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• Subsequent courses as needed: 12 mg/day on 3 consecutive days 12 months after any prior course	
Injectable therapies		
glatiramer (Copaxone®, Glatopa®)	20 mg subcutaneously once daily or 40 mg subcutaneously three times weekly	20 mg/day or 40 mg three times per week
interferon beta-1a (Avonex®, Rebif®)	Avonex®: 30 mcg intramuscularly weekly Rebif®: 22 mcg or 44 mcg subcutaneously three times weekly	Avonex®: 30 mcg/week Rebif®: 44 mcg three times per week
interferon beta-1b (Betaseron®, Extavia®)	250 mcg subcutaneously every other day	250 mg every other day
peginterferon beta-1a (Plegridy®)	125 mcg subcutaneously every 2 weeks	125 mcg/2 weeks
Oral therapies		
monomethyl fumarate (Bafiertam™)	Initial: 95 mg orally twice daily; after 7 days, increase to the maintenance dose of 190 mg orally twice daily.	380mg/day
diroximel fumarate (Vumerity®)	Starting: 231 mg orally twice daily for 7 days Maintenance: 462 mg orally twice daily	924 mg/day
teriflunomide (Aubagio®)	7 mg or 14 mg orally daily	14 mg/day
fingolimod (Gilenya™)	0.5 mg orally daily	0.5 mg/day
siponimod (Mayzent®)	Day 1 and 2: 0.25 mg orally once daily Day 3: 0.5 mg orally once daily Day 4: 0.75 mg orally once daily For CYP2C9 genotypes *1/*1, *1/*2, or *2/*2: Day 5: 1.25 mg orally once daily Day 6 & onward: 2 mg orally once daily For CYP2C9 genotypes *1/*3 or *2/*3: Day 5 & onward: 1 mg orally once daily	2 mg/day
ozanimod (Zeposia®)	Days 1-4: 0.23 mg orally once daily Days 5-7: 0.46 mg orally once daily Day 8 & onward: 0.92 mg orally once daily	0.92 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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 orally twice daily (approximately 12 hours apart)	20 mg/day

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

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 August 20, 2021.
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. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed August 20, 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(17): 777-788. Full guideline available at: https://www.aan.com/Guidelines/home/GetGuidelineContent/904. Accessed August 20, 2021.
4. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Accessed August 20, 2021.

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
Policy was reviewed. 1. Initial Approval Criteria I.A.2, trial and failure criteria, was updated from requiring member to try/fail at least two other therapies to requiring member to try/fail at least one other therapy; possible therapies to try were updated to include "(Avonex®, Betaseron®, Copaxone®, Vumerity®, Bafiertam®, Kesimpta®)". 2. Initial approval criteria I.A.4 was updated to add,"Member..... dimethyl fumarate." 3. Appendix A was updated to remove abbreviations PO, IM, IV, and SC. 4. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.". 5. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand	08/20/2021	09/14/2021

name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 6. References were reviewed and updated.		