Medication Policy Manual | **Policy No:** dru299

Topic: Tecfidera®, dimethyl fumarate | **Date of Origin:** May 16, 2013

Committee Approval Date: December 16, 2016 | **Next Review Date:** December 2017

Effective Date: January 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Dimethyl fumarate (Tecfidera) is an oral medication used for the treatment of multiple sclerosis. It works by helping to prevent nerve cells from inflammation and damage.

Policy/Criteria

I. Most contracts require prior authorization approval of dimethyl fumarate (Tecfidera) prior to coverage. Dimethyl fumarate (Tecfidera) may be considered medically necessary in patients with a definitive diagnosis of a relapsing form of multiple sclerosis (relapsing-remitting or secondary progressive multiple sclerosis) that has been established by a specialist in neurology or multiple sclerosis.

II. Administration, Quantity Limitations, and Authorization Period

- **A.** OmedaRx considers dimethyl fumarate (Tecfidera) to be a self-administered medication.
- **B.** When prior authorization is approved, dimethyl fumarate (Tecfidera) may be authorized in quantities of 60 capsules per month.
- **C.** Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Dimethyl fumarate (Tecfidera) is considered investigational when used concomitantly with other disease-modifying multiple sclerosis therapies (see *Appendix A*).

IV. Dimethyl fumarate (Tecfidera) is considered investigational when used for all other conditions, including but not limited to:

- **A.** Primary progressive multiple sclerosis (PPMS)
- **B.** Progressive-relapsing multiple sclerosis (PRMS)
- **C.** Psoriasis

Position Statement

- Dimethyl fumarate (Tecfidera) is an oral disease-modifying therapy used in the treatment of relapsing forms (relapsing-remitting and secondary progressing) of multiple sclerosis (MS) where it was found to decrease the frequency of MS attacks relative to placebo.
- There is no reliable evidence that dimethyl fumarate (Tecfidera) is safer or more effective than other disease-modifying medications used in the treatment of MS. Published clinical trials have only directly compared it with placebo.
- The safety and effectiveness of dimethyl fumarate (Tecfidera) when used in combination with other disease-modifying MS medications has not been established.
- The most common adverse effects associated with dimethyl fumarate (Tecfidera) include flushing and gastrointestinal effects such as nausea and diarrhea. Dimethyl fumarate (Tecfidera) contains a warning for progressive multifocal leukoencephalopathy (PML).

- Routine monitoring of blood counts is recommended before starting and periodic-ally during therapy because it may lower WBC count.
- Dimethyl fumarate (Tecfidera) is approved in doses of 240 mg taken twice daily. Higher doses have not been found to be more effective.

Clinical Efficacy

- Dimethyl fumarate (Tecfidera) has been shown to lower the rate of MS attacks relative to placebo. It also lowers the rate of disability progression, but the evidence is of low quality.
- A 2015 Cochrane review analyzed results from two pivotal phase 3 studies comparing dimethyl fumarate (Tecfidera) versus placebo. The authors concluded that there is moderate quality evidence that dimethyl fumarate (Tecfidera) reduces the number of patients who experience a relapse and overall annualized relapse rate compared to placebo. A statistically significant reduction in disability progression was also observed in patients who received dimethyl fumarate (Tecfidera), but the quality of evidence was appraised as low quality for this outcome. [1]
    * Glatiramer acetate was employed as an active comparator in one of the pivotal studies. When study dropouts were taken into account, differences between dimethyl fumarate (Tecfidera) and glatiramer acetate were not statistically significant. [1]
- There is no evidence directly comparing dimethyl fumarate (Tecfidera) with other disease-modifying MS therapies.
- Dimethyl fumarate (Tecfidera) has not been incorporated into national MS treatment guidelines.

Use of Dimethyl Fumarate (Tecfidera) in Other Conditions

- Dimethyl fumarate (Tecfidera) is being studied in plaque psoriasis; however, there are currently no well-conducted, published clinical trials evaluating its efficacy in this condition. [2]
- Dimethyl fumarate (Tecfidera) has not been studied in primary progressive MS, or progressive-relapsing MS.

Background on Multiple Sclerosis (MS) [3]

- There are four clinical courses of multiple sclerosis (characterized in Table 1 below).
- Relapsing-remitting multiple sclerosis accounts for up to 85% of cases.

Table 1: Multiple Sclerosis Forms/Clinical Course Definitions [3]	
Relapsing-remitting (RRMS)	Characterized by acute relapses that are followed by some degree of recovery; patients do not develop worsening of disability between relapses. The American Academy of Neurology (AAN) defines RRMS as the first clinical course of MS and is characterized by self-limited attacks of neurologic dysfunction. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, most patients experience a recovery of function that is often (but not always) complete. Between attacks the patient is neurologically and symptomatically stable.
Secondary progressive (SPMS)	Defined as sustained progression of physical disability occurring separately from relapses, in patients who previously had RRMS. The AAN defines SPMS as the second clinical course which begins as RRMS, but at some point the attack rate is reduced and the course becomes characterized by a steady deterioration in function unrelated to acute attacks.
Primary progressive (PPMS)	Defined as progression of disability from onset without superimposed relapses. The AAN defines PPMS as the third clinical type characterized by a steady decline in function from the beginning without acute attacks.
Progressive relapsing (PRMS)	Defined as primary progressive patients who develop acute relapses well after disease onset. The AAN defines PRMS as the fourth clinical type which also begins with a progressive course although these patients also experience occasional attacks.

Safety

- The most common (incidence $\geq$ 10% and $\geq$ 2% versus placebo) adverse effects associated with dimethyl fumarate (Tecfidera) include: flushing, abdominal pain, diarrhea, and nausea. [4]
- Approximately 6% of patients taking dimethyl fumarate (Tecfidera) in clinical studies experienced abnormally low (< 0.5x 10^9/L) lymphocyte counts while on therapy. However, there was no increased risk of serious infections observed in these patients.[4]
- Dimethyl fumarate (Tecfidera) contains a warning for progressive multifocal leukoencephalopathy (PML). Cases of PML have been reported in an extension study and the post-marketing setting. The majority of cases occurred in patients with low lymphocyte counts. Interruption of dimethyl fumarate (Tecfidera) should considered in patients with lymphocyte counts less than 0.5 x 10^9/L persisting for more than six months.

Dosing and Administration

- Dimethyl fumarate (Tecfidera) delayed-release capsules are dosed at 120 mg orally twice daily for one week, then 240 mg orally twice daily, thereafter.
- Higher doses of dimethyl fumarate (Tecfidera) were not associated with additional benefit, but may be associated with more side effects.
- Complete blood counts, including lymphocyte counts, are recommended before starting therapy, annually, and when clinically indicated.

Appendix A: FDA-Approved Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS)
Alemtuzumab (Lemtrada®)
Daclizumab (Zinbryta™)
Dimethyl fumarate (Tecfidera®)
Fingolimod (Gilenya®)
Glatiramer acetate (Copaxone®)
Interferon beta-1a (Avonex®, Rebif®)
Interferon beta-1b (Betaseron®, Extavia®)
Mitoxantrone (Novantrone®)
Natalizumab (Tysabri®)
Peginterferon beta-1a (Plegridy®)
Teriflunomide (Aubagio®)

Cross References
Aubagio®, teriflunomide, Medication Policy Manual, Policy No. 283
Copaxone®, glatiramer acetate, Medication Manual, Policy No. 412
Gilenya®, fingolimod, Medication Manual, Policy No. 229
Lemtrada®, alemtuzumab, Medication Manual, Policy No. 381
Non-preferred interferon beta products for MS, Medication Manual, Policy No. 108
Plegridy®, peginterferon beta-1a, Medication Policy Manual, policy No.376
Preferred interferon beta products for MS, Medication Policy Manual, Policy No. 000
Tysabri®, natalizumab, Medication Manual, Policy No. 111
Zinbryta™, daclizumab, Medication Manual, Policy No. 465

Codes	Number	Description
HCPCS	J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified
HCPCS	J2323	Injection, natalizumab, 1 mg
ICD-10	G35	Multiple Sclerosis

References

1. Xu, Z, Zhang, F, Sun, F, Gu, K, Dong, S, He, D. Dimethyl fumarate for multiple sclerosis. *The Cochrane database of systematic reviews*. 2015;4:CD011076. PMID: 25900414
2. Efficacy Study on Dimethyl Fumarate to Treat Moderate to Severe Plaque Psoriasis. [cited 11/11/2015]; Available from: https://clinicaltrials.gov/ct2/show/NCT01815723
3. Goodin, DS, Frohman, EM, Garmany, GP, Jr., et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002 Jan 22;58(2):169-78. PMID: 11805241
4. Behm, BW, Bickston, SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. *The Cochrane database of systematic reviews*. 2008 Jan 23(1):CD006893. PMID: 18254120

Revision Date	Revision Summary
12/16/2016	Removed step therapy requirements
12/11/2015	Revised definition of interferon beta ineffectiveness from “two clinical relapses in the past 12 months” to “one clinical relapse in the past 12 months.”