Formulary Drug Reviews

Dimethyl Fumarate

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Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with *The Formulary Monograph Service*. Through the cooperation of *The Formulary, Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, call *The Formulary* at 800-322-4349. The September 2013 monograph topics are trametinib, simeprevir, paroxetine mesylate, and empagliflozin. The DUE/MUE is on aripiprazole.

Generic Name:	Dimethyl fumarate (BG-12) delayed-release capsules
Proprietary Name:	Tecfidera (Biogen Idec)
Approval Rating:	1S
Therapeutic Class:	Immunomodulators
Similar Drugs:	None
Sound- or Look- Alike Names:	Dimethylglycine

INDICATIONS

Dimethyl fumarate is approved for the treatment of relapsing forms of multiple sclerosis (MS).^{1,2} Other oral therapies for the treatment of MS include teriflunomide (*Aubagio*), approved for the treatment of patients with relapsing forms of MS, and fingolimod (*Gilenya*), approved for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability.^{3,4}

MS is a chronic autoimmune, inflammatory neurological disease that involves the myelin and axons in the central nervous system (CNS). No drug has been

proven to cure MS, but many drugs (eg, alemtuzumab, beta-interferons, cladribine, daclizumab, dalfampridine, fingolimod, glatiramer acetate, laquinimod, mitoxantrone, natalizumab, ocrelizumab, teriflunomide) with different pharmacologic effects have been used to help decrease symptoms and the frequency of exacerbations.⁵⁻¹³ The ideal drug would decrease disease symptoms, decrease the frequency of exacerbations, slow or stop the progression of the disease, reverse pre-existing neurological damage, and improve the patient's quality of life.^{10,14} The course of MS is variable and unpredictable; MS is grouped into the following 4 major categories based on the course of the disease.^{5,15}

Relapsing-Remitting Multiple Sclerosis

Relapsing-remitting MS is the most common form, accounting for about 85% of all MS diagnoses. It is characterized by unpredictable relapses or exacerbations of symptoms or by the appearance of new symptoms followed by periods of remission. During periods of remission, symptoms may improve or even disappear.^{5,15}

Secondary Progressive Multiple Sclerosis

Some patients with relapsing-remitting MS advance to a steadily progressive form of the disease. In

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Table 1. FDA-approved therapies for relapsing multiple sclerosis with corresponding mechanism of action and pharmacologic category^{1,3,4,11,40-42}

	Mechanism of action	Pharmacologic category
Dimethyl fumarate	Activation of the Nrf2 pathway	Immunomodulator
Fingolimod	Prevents the release of lymphocytes from lymph nodes, thus reducing the number of lymphocytes and inflammation within the CNS	Sphingosine 1-phosphate receptor modulator
Glatiramer acetate	Induces and activates T-lymphocyte suppressor cells specific to myelin antigen and interferes with antigen-presenting function of immune cells opposing pathogenic T-cell function	Immunomodulator
Interferon beta-1a	Alters the expression and response of surface antigens and enhances immune cell activities	Interferon
Interferon beta-1b	Alters the expression and response of surface antigens and enhances immune cell activities	Interferon
Mitoxantrone	Inhibits B-cell, T-cell, and macrophage proliferation; impairs antigen presentation secretion of interferon gamma, tumor necrosis factor- α , and interleukin 2	Antineoplastic agent, anthracenedione
Natalizumab	Blocks T-lymphocyte migration into the CNS	Monoclonal antibody, selective adhesion-molecule inhibitor (alpha-4-adhesin)
Teriflunomide	Inhibits B-cell and T-cell proliferation, activation, and production of cytokines	Dihydroorotate dehydrogenase inhibitor

Note: CNS = central nervous system; FDA = US Food and Drug Administration.

these patients, the severity of the disease worsens over time. These patients may or may not experience periods of remission or decreased severity of symptoms.^{5,15}

Primary Progressive Multiple Sclerosis

Patients with primary progressive MS have a gradual worsening of symptoms throughout the course of the disease; the primary progressive form accounts for 10% to 15% of MS diagnoses. These patients do not experience remissions but may experience periods during which their symptoms do not continue to worsen.^{5,15}

Progressive Relapsing Multiple Sclerosis

Progressive relapsing is the least common form of MS and is characterized by disease that progresses from the beginning, with periods of worsening symptoms (exacerbations) and no periods of remission.^{5,15}

CLINICAL PHARMACOLOGY

Dimethyl fumarate is a fumaric acid ester. Its active metabolite is monomethyl fumarate. The exact mechanism of action of dimethyl fumarate is

unknown. The drug and its metabolite are thought to work by activation of the nuclear factor (erythroid-derived 2)-like (Nrf2) pathway, which is involved in the cellular response to oxidative stress.^{1,16} Protection of the neuron from oxidative metabolic stress may be provided by increased levels of antioxidant proteins. In addition, dimethyl fumarate may have anti-inflammatory effects because of its blockade of nuclear factor kappa-B and its ability to prevent release of proinflammatory cytokines, lymphocyte activation, and differentiation of antigen-presenting cells.^{9,16-22} See Table 1 for a comparison of pharmacologic effects of the various drugs used for the treatment of MS.

PHARMACOKINETICS

Dimethyl fumarate is available as a delayed-release capsule. Once released from the capsule, the drug undergoes rapid hydrolysis to its active metabolite, monomethyl fumarate. Because the conversion occurs quickly and before systemic circulation, dimethyl fumarate is not detectable in quantifiable amounts in plasma, and all available pharmacokinetic information is related to monomethyl fumarate.¹

The median time to peak plasma concentration following oral administration of the delayed-release capsule is 2 to 2.5 hours. Changes in peak plasma concentrations and area under the curve (AUC) between 120 and 360 mg are approximately dose proportional. The mean peak plasma concentration of monomethyl fumarate in patients with MS taking dimethyl fumarate 240 mg twice daily with food is 1.87 mg/L, and the AUC is 8.2 mg•h/L.¹

Administration with a high-fat, high-caloric meal does not affect the AUC of monomethyl fumarate, but it does decrease its peak plasma concentration by 40%. Peak plasma concentration is delayed by 3.5 hours (from 2 to 5.5 hours). However, administration with food decreases the incidence of flushing by 25%.¹

Monomethyl fumarate is metabolized by the tricarboxylic acid cycle to carbon dioxide, fumaric acid, citric acid, and glucose. The cytochrome P450 (CYP-450) system is not involved in the metabolism of dimethyl fumarate or monomethyl fumarate. Elimination as carbon dioxide is the main route of elimination (approximately 60% of the dose). Renal elimination accounts for 16% of the dose, and fecal elimination accounts for 1% of the dose.¹

The terminal half-life of monomethyl fumarate is 1 hour.¹

COMPARATIVE EFFICACY

Indication: Relapsing-Remitting Multiple Sclerosis

Studies

Drug: Dimethyl Fumarate vs Placebo

Reference: Kappos L, et al, 2008²³

Study Design: Randomized, placebo-controlled, dose-ranging, multicenter, phase 2b study

Study Funding: Biogen Idec

Patients: 257 adults with relapsing-remitting MS from the European Union, Russian Federation, Switzerland, and Turkey. Previously used drugs for the treatment of MS were discontinued or not allowed, depending on the agent.

Intervention: In phase 1, all patients received orally administered dimethyl fumarate 120 mg once daily, dimethyl fumarate 120 mg 3 times daily, dimethyl fumarate 240 mg 3 times daily, or placebo for 24 weeks. The second phase of the study was a dose-blinded safety assessment of dimethyl fumarate. Patients who previously received dimethyl fumarate were kept on the same dosage, and all placebo-treated patients were switched to dimethyl fumarate 240 mg 3 times daily for an additional 24

weeks of therapy. Patients chosen to receive dimethyl fumarate 240 mg 3 times daily were initially given dimethyl fumarate 120 mg 3 times daily for 1 week and were then switched to 240 mg 3 times daily the next week.

Results:

Primary Endpoint(s):

- Total number of new gadolinium-enhancing (Gd+) lesions at weeks 12, 16, 20, and 24: The number of new Gd+ lesions from weeks 12 to 24 was 1.4 with dimethyl fumarate 240 mg 3 times daily versus 4.5 with placebo ($P < .001$). The number of new Gd+ lesions with dimethyl fumarate 120 mg once daily and dimethyl fumarate 120 mg 3 times daily was 3.3 ($P < .266$ vs placebo) and 3.1 ($P < .068$ vs placebo), respectively.

Secondary Endpoint(s):

- Fewer cumulative new Gd+ lesions occurred (3.7 vs 6.6; 48% reduction; $P = .002$) with dimethyl fumarate 240 mg 3 times daily than with placebo from weeks 4 to 24. The number of new Gd+ lesions with dimethyl fumarate 120 mg once daily and dimethyl fumarate 120 mg 3 times daily was 6.2 ($P = .943$ vs placebo) and 6.7 ($P = .801$ vs placebo), respectively.
- Number of new or enlarging T2-hyperintense lesions at week 24 was 2.2 with dimethyl fumarate 240 mg 3 times daily versus 4.2 with placebo ($P < .001$).
- Number of new T1-hypointense lesions was 0.8 with dimethyl fumarate 240 mg 3 times daily versus 1.7 with placebo ($P = .014$).
- Annualized relapse rate was 0.44 with dimethyl fumarate 240 mg 3 times daily versus 0.65 with placebo ($P = .272$).
- No differences were observed between the 2 lower dosages of dimethyl fumarate and placebo for all parameters.
- Clinical effects appeared to be maintained for at least 1 year.

Comments: The highest dimethyl fumarate dosage (240 mg 3 times daily) appeared to be well tolerated and produced better clinical outcomes than placebo. A subgroup analysis of this study population found that the 240 mg 3 times daily dosage was effective, based on a reduction in number of new Gd+ lesions from weeks 12 to 24 across various subgroups tested. The incidence of new Gd+ lesions compared with placebo was reduced by 74% in patients with an Expanded Disability Status Scale score of 2.5 or less and by 63% in those with

a score greater than 2.5; by 80% in those with no pre-existing Gd+ lesions and by 55% in those with more than 1 pre-existing Gd+ lesion; by 49% in those younger than 40 years and by 89% in those 40 years or older; by 81% in female patients; and by 81% in those with a disease duration of 6 years or less and by 54% in those with a disease duration of longer than 6 years.²⁴ Another subgroup analysis retrospectively evaluated the magnetic resonance imaging (MRI) scans from this study. The percentage of Gd+ lesions that evolved to T1-hypointense lesions was 34% lower with dimethyl fumarate treatment than with placebo: 29% with dimethyl fumarate and 44% with placebo, with an odds ratio of 0.51 (95% confidence interval [CI], 0.43 to 0.61; $P < .001$).²⁵

Limitations: The study was powered to evaluate various dosages of dimethyl fumarate but not powered to evaluate the impact of the drug on the frequency of relapses.

Reference: Gold R, et al, 2012 (DEFINE study)²⁶⁻³⁰

Study Design: Randomized (1:1:1), placebo-controlled, multicenter, phase 3 study

Study Funding: Biogen Idec

Patients: 1,237 adults with relapsing-remitting MS from the European Union, United States, Canada, and other countries were enrolled; 1,234 received at least 1 dose of the study drug (intent-to-treat cohort). Approximately 40% of patients had previously been treated with an approved therapy for relapsing-remitting MS. The proportion of patients completing the study was similar in both the placebo and dimethyl fumarate groups (78% in the placebo group and 77% in the dimethyl fumarate group). The mean duration of study participation was 83.9 weeks in all groups.

Intervention: Oral administration of dimethyl fumarate 240 mg twice daily, dimethyl fumarate 240 mg 3 times daily, or placebo for 2 years. All patients were eligible to switch to an alternative therapy for MS if they had completed 48 weeks of study treatment and had 1 or more confirmed relapse after 24 weeks. Patients could also switch at any time if they had confirmed progression of disability. If a patient was switched to an alternative therapy, all data from before the switch were used for analysis of the clinical endpoints.

Results:

Primary Endpoint(s):

- Proportion of relapsing patients at 2 years in the intent-to-treat cohort:

- Based on Kaplan-Meier estimates, 27% of patients in the twice-daily and 26% in the 3-times-daily dimethyl fumarate groups had at least 1 relapse, compared with 46% in the placebo group ($P < .01$, for both comparisons).
- 49% reduction with dimethyl fumarate 240 mg twice daily versus placebo (hazard ratio [HR], 0.51; 95% CI, 0.4 to 0.66; $P < .001$).
- 50% reduction with dimethyl fumarate 240 mg 3 times daily versus placebo (HR, 0.5; 95% CI, 0.39 to 0.65; $P < .001$).
- Time to first relapse in the 25th percentile was 38 weeks in the placebo group, 87 weeks in the twice-daily dimethyl fumarate group, and 91 weeks in the 3-times-daily dimethyl fumarate group.

Secondary Endpoint(s):

- Odds of an increase in the number of Gd+ lesions at 2 years decreased by 90% with dimethyl fumarate twice daily and by 73% with dimethyl fumarate 3 times daily ($P < .001$, for both comparisons).
- Number of new or enlarging T2-hyperintense lesions was decreased by 85% with dimethyl fumarate twice daily and by 74% with dimethyl fumarate 3 times daily ($P < .001$, for both comparisons).
- Number of new T1-hypointense lesions was decreased by 72% with dimethyl fumarate twice daily and by 63% with dimethyl fumarate 3 times daily.
- Relative reduction in annualized relapse rate:
 - 53% with dimethyl fumarate 240 mg twice daily versus placebo (HR, 0.47; 95% CI, 0.37 to 0.61; $P = .01$).
 - 48% with dimethyl fumarate 240 mg 3 times daily versus placebo (HR, 0.52; 95% CI, 0.5 to 0.67; $P = .01$).
- Disability progression risk was lower with both dosages of dimethyl fumarate compared with placebo: 38% reduction (HR, 0.63; 95% CI, 0.44 to 0.87; $P = .005$) with dimethyl fumarate twice daily and 34% reduction (HR, 0.66; 95% CI, 0.48 to 0.92; $P = .01$) with dimethyl fumarate 3 times daily. The estimated proportion with progression of disability was 27% with placebo, 16% with twice-daily dimethyl fumarate, and 18% with 3-times-daily dimethyl fumarate.
- MRI analysis showed reduced brain atrophy and lesion volume with dimethyl fumarate therapy from 6 months to 2 years.

- Percentage of patients who switched therapy was low in all groups (13% in the placebo group, 6% in the dimethyl fumarate twice-daily group, and 5% in the dimethyl fumarate 3-times-daily group).

Comments: Dimethyl fumarate is more effective than placebo in decreasing the relapse rate in patients with relapsing-remitting MS over 2 years. The incidences of new Gd+ lesions and disability progression are decreased with dimethyl fumarate therapy. All sensitivity analyses were consistent with those found in the primary efficacy analysis. Both dosages of dimethyl fumarate produced improvements in patients' reported health-related quality of life compared with placebo.²⁹ A subgroup analysis of this study population found that both dosages had a consistent effect on relapse and disability parameters compared with placebo. The HR for the risk of relapse over 2 years was 0.52 (95% CI, 0.38 to 0.71) with dimethyl fumarate twice daily and 0.51 (95% CI, 0.37 to 0.7) with dimethyl fumarate 3 times daily in patients who had 1 or fewer relapses in the year prior to study entry. In the group of patients who experienced 2 or more relapses during the year prior to study entry, the HR was 0.51 (95% CI, 0.34 to 0.77) with twice-daily dosing and 0.49 (95% CI, 0.32 to 0.74) with 3-times-daily dosing.³¹ Another subgroup analysis found that the proportion of disease-free patients over 2 years based on clinical parameters was 63% with dimethyl fumarate twice daily, 59% with dimethyl fumarate 3 times daily, and 39% with placebo ($P < .001$); based on radiologic findings, the proportion of disease-free patients over 2 years was 45%, 39%, and 27% ($P < .05$), respectively. The proportion of disease-free patients using a combination of clinical and radiologic findings was 28% with dimethyl fumarate twice daily, 26% with dimethyl fumarate 3 times daily, and 15% with placebo ($P < .05$).³²

Limitations: Most of the subgroup analyses have been published only as meeting abstracts or posters.

Drug: Dimethyl Fumarate vs Glatiramer Acetate vs Placebo

- **Reference:** Fox RJ, et al, 2012 (CONFIRM study)^{26,27,33-36}
- **Study Design:** Randomized (1:1:1:1), placebo-controlled, active comparator, multicenter study
- **Study Funding:** Biogen Idec

- **Patients:** 1,430 adults with relapsing-remitting MS from the European Union, United States, Canada, and other countries; 1,417 received at least 1 dose of the study drug (intent-to-treat cohort). Approximately 29% of patients had previously been treated with an approved therapy for relapsing-remitting MS. The proportion of patients completing the study was 80%. Mean duration of study participation was approximately 86 weeks.
- **Intervention:** All patients received oral medication 3 times daily and a subcutaneous injection once daily for 96 weeks. Patients were randomized to treatment with oral dimethyl fumarate 240 mg twice daily, oral dimethyl fumarate 240 mg 3 times daily, injectable glatiramer acetate 20 mg once daily, or placebo. All patients were eligible to switch to an alternative therapy for MS if they had completed 48 weeks of study treatment and had 2 confirmed relapses. Patients could also switch at any time if they had confirmed progression of disability. If a patient was switched to an alternative therapy, all data from before the switch were used for analysis of the clinical endpoints.

Results:

Primary Endpoint(s):

- Annualized relapse rate decreased by 44% with dimethyl fumarate twice daily and by 51% with dimethyl fumarate 3 times daily compared with placebo ($P < .001$) at 2 years in the intent-to-treat cohort. Glatiramer acetate decreased the relapse rate by 29% ($P < .01$ vs placebo).
- Based on Kaplan-Meier estimates, 29% of patients in the twice-daily dimethyl fumarate group, 24% in the 3-times-daily dimethyl fumarate group, and 32% in the glatiramer acetate group had at least 1 relapse, compared with 41% in the placebo group.

Secondary Endpoint(s):

- The proportion of patients who relapsed decreased by 34% with dimethyl fumarate twice daily ($P < .002$), by 45% with dimethyl fumarate 3 times daily ($P < .001$), and by 29% with glatiramer acetate ($P = .01$) compared with placebo.
- Disability progression was not reduced with any of the treatment groups compared with placebo: HR of 0.79 (95% CI, 0.52 to 1.19) with dimethyl fumarate twice daily, HR of 0.76 (95% CI, 0.5 to 1.16) with dimethyl fumarate 3 times

daily, and HR of 0.93 (95% CI, 0.63 to 1.37) with glatiramer acetate.

- Number of new or newly enlarging T2-hyperintense lesions decreased by 71% with dimethyl fumarate twice daily ($P < .001$) and by 73% with dimethyl fumarate 3 times daily ($P < .001$) compared with placebo, whereas glatiramer acetate produced a 54% reduction ($P < .001$ vs placebo).
- New T1-hypointense lesions decreased by 57% with dimethyl fumarate twice daily ($P < .001$), by 65% with dimethyl fumarate 3 times daily ($P < .001$), and by 41% with glatiramer acetate ($P < .002$) compared with placebo.

Comments: Dimethyl fumarate is more effective than placebo in decreasing the relapse rate in patients with relapsing-remitting MS over 2 years. The incidence of new Gd+ lesions was also decreased with dimethyl fumarate therapy. Both dosages of dimethyl fumarate produced similar improvements and appear more effective on these parameters than glatiramer acetate therapy.

Limitations: The study was not powered for a direct comparison of glatiramer acetate and dimethyl fumarate. Instead, the glatiramer acetate group is an active comparator, but all statistical testing was done against placebo.

There are no head-to-head comparisons between dimethyl fumarate and either fingolimod or teriflunomide.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

There are no contraindications.¹

Warnings and Precautions

Lymphopenia may occur during dimethyl fumarate therapy. Mean lymphocyte counts decreased by approximately 30% during the first year of therapy in clinical trials and then remained stable. When dimethyl fumarate therapy was discontinued, mean lymphocyte count increased within 4 weeks but did not return to baseline. The incidence of lymphocyte counts less than $0.5 \times 10^9/L$ was 6% in dimethyl fumarate-treated patients and less than 1% in placebo-treated patients. However, the incidence of infections (60% vs 58%, respectively) and serious infections (2% vs 2%, respectively) was similar in both groups, and no cases of serious infections occurred in patients with lymphocyte counts less than $0.8 \times 10^9/L$. Routine complete blood cell (CBC) counts should be performed throughout therapy. Withholding dimethyl fumarate therapy

should be considered if the patient develops a serious infection.¹

Flushing (eg, warmth, redness, itching, and/or burning sensation) may occur with dimethyl fumarate therapy. Flushing occurred in 40% of dimethyl fumarate-treated patients and generally began soon after therapy initiation; it was most commonly classified as mild to moderate in severity and improved over time. Administration with food decreased the incidence of flushing in some patients. Flushing prompted discontinuation of therapy in 3% of patients and was reported to be serious and required hospitalization in less than 1%.¹

Dimethyl fumarate is classified in Pregnancy Category C; there are no adequate and well-controlled studies in pregnant women. Animal studies found problems with offspring survival, growth, sexual maturation, and neurobehavioral functions. If a pregnancy occurs during treatment with dimethyl fumarate therapy, the patient should be encouraged to enroll in the *Tecfidera* Pregnancy Registry.¹

It is not known whether dimethyl fumarate is excreted in human milk.¹

Safety and effectiveness in pediatric patients have not been established.¹ A postmarketing study in pediatric patients 10 to 17 years of age is required by the US Food and Drug Administration (FDA).²

See Table 2 for a comparison of contraindications, warnings, and precautions associated with the approved oral MS drugs.

ADVERSE REACTIONS

The most common adverse reactions associated with dimethyl fumarate therapy (frequency of at least 10% and at least a 2% higher incidence than placebo) include flushing, abdominal pain, diarrhea, and nausea.^{1,27,36} Flushing and GI reactions (abdominal pain, diarrhea, and nausea) occur more frequently at initiation of therapy and may decrease over time.^{1,27,36} The most common adverse reactions reported with dimethyl fumarate therapy are summarized in Table 3.

Flushing generally occurred within 30 minutes of drug administration, subsided within 90 minutes, and decreased with continued therapy.^{23,37} Pretreatment with aspirin can decrease the incidence and severity of flushing, but this method is not mentioned in the product labeling.^{1,37} Instead, product labeling recommends administration with food.¹

Elevations in hepatic transaminases may occur, generally within the first 6 months of therapy, and most patients had elevations of less than 3 times the upper limit of normal. Discontinuation because of

Table 2. Contraindications, warnings, and precautions associated with the approved oral multiple sclerosis drugs^{1,3,4}

	Dimethyl fumarate	Fingolimod	Teriflunomide
<i>Contraindications</i>			
Severe hepatic impairment			X
Pregnancy			X
Current leflunomide treatment			X
Severe cardiovascular event (eg, myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, class III/IV heart failure) within the previous 6 months		X	
History of or current Mobitz type II second- or third-degree atrioventricular block or sick sinus syndrome, unless patient has a functioning pacemaker		X	
Baseline QTc interval $\geq$ 500 ms		X	
Treatment with class Ia or III antiarrhythmic drugs		X	
<i>Warnings and precautions</i>			
Atrioventricular block		X	
Blood pressure increased		X	X
Bone marrow disease; use not recommended			X
Bradyarrhythmia block		X	
Hepatotoxicity		X	X
Hyperkalemia			X
Interstitial lung disease or worsening of pre-existing interstitial lung disease			X
Lung function decreased		X	
Macular edema		X	
Method for accelerated elimination of drug			X
Peripheral neuropathy			X
Acute renal failure			X
Concurrent use of immunosuppressive or immunomodulating therapies		X	X
Severe immunodeficiency; use not recommended			X
White blood cell count decrease	X	X	X
Risk of infection		X	X
Infections (severe, uncontrolled); use not recommended			X
Tuberculosis screening			X
Varicella zoster virus antibody testing/vaccination		X	
Vaccination (live vaccines); use not recommended			X
Risk of malignancy			X
Skin reactions			X
Use in women of childbearing potential		X	X
Flushing	X		
Pregnancy	Category C	Category C	Category X
Breast-feeding	Caution	Not recommended	Not recommended

Table 3. Incidence of most common adverse reactions (incidence at least 2% higher than placebo) associated with dimethyl fumarate 240 mg twice daily in placebo-controlled trials (studies 1 and 2)¹

Adverse reactions	Dimethyl fumarate (n = 769)	Placebo (n = 771)
Flushing	40%	6%
Abdominal pain	18%	10%
Diarrhea	14%	11%
Nausea	12%	9%
Vomiting	9%	5%
Pruritus	8%	4%
Rash	8%	3%
Albumin urine present	6%	4%
Dyspepsia	5%	3%
Erythema	5%	1%
AST increased	4%	2%
Lymphopenia	2%	<1%

elevated hepatic transaminases occurred in less than 1% in both dimethyl fumarate- and placebo-treated patients.¹

Some patients may experience transient increases in mean eosinophil counts during the first 2 months of therapy.¹

The incidence of infections was similar in the dimethyl fumarate- and placebo-treated patients in the DEFINE and the CONFIRM studies.^{30,36} The incidence of infection in the DEFINE study was 65% in the placebo group, 64% in the twice-daily dimethyl fumarate group, and 68% in the 3-times-daily dimethyl fumarate group. The most common infections were nasopharyngitis, upper respiratory tract infection, urinary tract infection, and influenza.³⁰ The incidence of infection in the CONFIRM study was 50% in the placebo group, 65% in the dimethyl fumarate groups, and 50% in the glatiramer acetate group. The most common infections were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, and gastroenteritis.³⁶

The incidence of renal adverse events was similar among treatment groups (21% with placebo, 22% with twice-daily dimethyl fumarate, and 25% with 3-times-daily dimethyl fumarate); there were no cases of renal failure in the DEFINE study, but there was a difference in the incidence of proteinuria.³⁰ Proteinuria occurred in 8% of placebo-treated patients, 9% of patients receiving twice-daily dimethyl fumarate, and 12% of patients receiving 3-times-daily dimethyl fumarate. Proteinuria was classified as mild and reversible and did not result in discontinuation of treatment.

See **Table 4** for a comparison of adverse reactions reported in the product labeling for the approved oral MS drugs.

Table 4. Adverse reactions (incidence of at least 10% and at least 2% higher than placebo for dimethyl fumarate) reported in the product labeling for approved oral multiple sclerosis drugs^{1,3,4a}

	Dimethyl fumarate	Placebo	Fingolimod	Placebo	Teriflunomide		
					7 mg	14 mg	Placebo
Abdominal pain	18%	10%					
ALT increased			14%	5%	12%	14%	7%
Alopecia					10%	13%	3%
Back pain			12%	7%			
Cough			10%	8%			
Diarrhea	14%	11%	12%	7%	15%	18%	9%
Flushing	40%	6%					
Headache			25%	23%	22%	19%	18%
Influenza			13%	10%	9%	12%	10%
Nausea	12%	9%			9%	14%	7%
Paresthesia					9%	10%	8%

^aResults are from placebo-controlled trials in varying populations with MS and not head-to-head comparative studies.

Table 5. Drug-drug interactions for the approved oral multiple sclerosis drugs^{1,3,4}

Drug interaction	Dimethyl fumarate ^a	Fingolimod	Teriflunomide
Antineoplastic, immunosuppressive, or immunomodulating therapies		X	
CYP1A2 substrates (eg, duloxetine, alosetron, theophylline, tizanidine)			X
CYP2C8 substrates (eg, repaglinide, paclitaxel, pioglitazone, rosiglitazone)			X
Drugs that slow heart rate or atrioventricular conduction (eg, beta-blockers, diltiazem)		X	
Ketoconazole		X	
Oral contraceptives			X
QT-prolonging drugs (eg, citalopram, chlorpromazine, haloperidol, methadone, erythromycin)		X	
Vaccines		X	X
Warfarin			X

^aNone reported in the product labeling for dimethyl fumarate.

DRUG INTERACTIONS

No drug-drug interactions have been identified.¹

Administration of aspirin 30 minutes before oral administration of dimethyl fumarate had no effect on the pharmacokinetics of monomethyl fumarate.¹

See Table 5 for a comparison of the drug-drug interactions reported for the approved oral MS drugs.

CBC counts should be measured at baseline (or at least within the last 6 months) and at least annually during therapy. Additional CBC counts should be obtained if clinically indicated.¹

See Table 6 for a comparison of recommended monitoring for oral MS drugs.

DOSING

The recommended starting dosage of dimethyl fumarate is 120 mg orally twice a day for 7 days. The dosage is then increased to the recommended maintenance dosage of 240 mg orally twice a day.¹

RECOMMENDED MONITORING

Patients should be monitored for improvement in symptoms and frequency and severity of relapses prior to and after starting dimethyl fumarate therapy.

Table 6. Recommended monitoring for the approved oral multiple sclerosis drugs^{1,3,4}

	Dimethyl fumarate	Fingolimod	Teriflunomide
Bilirubin		Within 6 mo prior to starting therapy	Within 6 mo prior to starting therapy
Blood pressure		Periodically throughout therapy	Prior to start of therapy and periodically throughout therapy
Complete blood cell count	Within 6 mo prior to starting therapy, annually, and as clinically indicated	Within 6 mo prior to starting therapy	Within 6 mo prior to starting therapy
Electrocardiogram		Prior to first dose and at the end of the first dose observation period	
Heart rate		During first dose and periodically throughout therapy	
Serum potassium			If symptomatic or in patients with acute renal failure
Serum transaminase		Within 6 mo prior to starting therapy	Within 6 mo prior to starting therapy; monitor monthly for 6 mo after starting therapy
Spirometric evaluation		When needed during therapy	

Table 7. Recommended dosing for the approved oral multiple sclerosis drugs^{1,3,4}

	Dimethyl fumarate	Fingolimod	Teriflunomide
Starting dosage	120 mg twice daily for 7 days	0.5 mg once daily	7 mg or 14 mg once daily
Maintenance dosage	240 mg twice daily	0.5 mg once daily	7 mg or 14 mg once daily
Food	With or without	With or without	With or without
Office monitoring required for first dose		X	

Dimethyl fumarate can be taken with or without food; however, administration with food may reduce the incidence of flushing. Capsules should be swallowed whole and intact and not crushed or chewed; the contents of an open capsule should not be sprinkled on food.¹ See Table 7 for a comparison of dosing recommendations for the approved oral MS drugs.

PRODUCT AVAILABILITY

The new drug application for dimethyl fumarate was submitted to the FDA in February 2012.³⁸ Dimethyl fumarate was approved by the FDA in March 2013.^{1,2}

Tecfidera is available as a hard gelatin delayed-release capsule containing 120 or 240 mg of dimethyl fumarate. Each capsule contains dimethyl fumarate plus the following inactive ingredients: microcrystalline cellulose, silicified microcrystalline cellulose, croscarmellose sodium, talc, silica colloidal silicon dioxide, magnesium stearate, triethyl citrate, and polysorbate 80. The capsule shell contains gelatin, titanium dioxide, FD&C Blue No. 1, methacrylic acid copolymer type A, methacrylic acid copolymer dispersion, simethicone, sodium lauryl sulphate, brilliant blue FCF, yellow iron oxide, and black iron oxide.¹

The 120 mg capsule is available in a 7-day bottle containing 14 capsules. The 240 mg capsule is available in a 30-day bottle containing 60 capsules. Both strengths are available in a 30-day starter pack containing a 7-day bottle of 120 mg capsules and a 23-day bottle of 240 mg capsules.¹

Dimethyl fumarate should be stored at 15°C to 30°C (59°F to 86°F). The capsules should be stored in the original container and protected from light. Once the bottle is opened, its contents should be discarded after 90 days.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for dimethyl fumarate or teriflunomide, whereas a REMS program is required for fingolimod.^{2,3,39}

Postmarketing requirements include an evaluation of the in vitro receptor binding of dimethyl fumarate

and its metabolite with various receptors; assessment of abuse potential with animals trained to discriminate the known drug of abuse from saline; juvenile rat toxicology study to model its potential effects in children; and a large, long-term, prospective observational study in adult patients with relapsing MS to determine the nature and incidence of various infections, malignancies, and serious adverse reactions.²

CONCLUSION

None of the drugs used for the treatment of MS are ideal. All drugs used in the treatment of MS have unique problems, but some have resulted in improvement in symptoms and decreased frequency of exacerbations. Dimethyl fumarate is another useful oral agent for the treatment of relapsing-remitting MS. Available data from phase 3 studies indicate that dimethyl fumarate is useful in decreasing the number of new lesions and the frequency of relapses. The head-to-head comparison of oral dimethyl fumarate and subcutaneous glatiramer acetate showed that both dimethyl fumarate and glatiramer acetate were more effective than placebo, whereas dimethyl fumarate monotherapy was more effective than glatiramer acetate monotherapy for the treatment of patients with relapsing-remitting MS. There are no comparisons of dimethyl fumarate with other oral drugs (fingolimod or teriflunomide) used for the treatment of relapsing-remitting MS. The key differences among the oral agents are the warnings, incidences of various adverse reactions, and dosing frequency associated with each drug. The key dimethyl fumarate warnings are regarding lymphopenia and flushing; fingolimod carries cardiovascular warnings (first-dose monitoring is required) and teriflunomide has been associated with hepatotoxicity and teratogenic effects. The most common adverse reactions reported with fingolimod include headache, influenza, diarrhea, back pain, liver transaminase elevation, and cough; teriflunomide adverse reactions include ALT elevation, alopecia, diarrhea, influenza, nausea, and paresthesia; and dimethyl fumarate adverse reactions include flushing,

abdominal pain, diarrhea, and nausea. Dosing frequency with fingolimod and teriflunomide is once daily, and dimethyl fumarate dosing frequency is twice daily. All 3 drugs can be given with or without food.

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Continuing Education Case Study Quiz

Goal—The goal of this program is to educate pharmacists about the use of dimethyl fumarate for the treatment of patients with multiple sclerosis (MS).

Objectives—At the completion of this program, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of dimethyl fumarate.
2. Discuss the risks associated with the use of dimethyl fumarate.
3. Discuss the potential benefit of dimethyl fumarate for an individual patient.
4. Apply the information on the use of dimethyl fumarate to a case study.

Key Words—dimethyl fumarate, immunomodulator, multiple sclerosis, new drugs

1. The US Food and Drug Administration (FDA)–approved indication for dimethyl fumarate is:
 - a. The treatment of moderate to severe psoriasis.
 - b. The treatment of relapsing forms of MS.
 - c. The treatment of primary progressive MS.
 - d. The treatment of secondary progressive MS.
2. Which of the following is the mechanism of action for dimethyl fumarate?
 - a. Activation of the nuclear factor (erythroid-derived 2)–like (Nrf2) pathway
 - b. Alteration of the expression and response of surface antigens and enhancement of immune cell activities
 - c. Inhibition of B-cell and T-cell proliferation and activation and inhibition of the production of cytokines
 - d. Prevention of the release of lymphocytes from lymph nodes, thus reducing the number of lymphocytes and inflammation within the central nervous system (CNS)
3. Monomethyl fumarate is an active metabolite of dimethyl fumarate.
 - a. True
 - b. False
4. Dimethyl fumarate is classified in Pregnancy Category:
 - a. B.
 - b. C.
 - c. D.
 - d. X.
5. Which of the following warnings/precautions are shared by the 3 oral MS medications dimethyl fumarate, fingolimod, and teriflunomide?
 - a. Blood pressure increase
 - b. Flushing
 - c. Hepatotoxicity
 - d. White blood cell count reduction
6. Which of the following is a drug interaction reported with dimethyl fumarate?
 - a. Decreased efficacy of concomitantly administered oral contraceptives
 - b. Increased concentrations of CYP1A2 substrates such as duloxetine and tizanidine
 - c. Increased risk of QT prolongation when administered with clarithromycin
 - d. No drug-drug interactions have been identified.
7. What are the most common side effects associated with dimethyl fumarate?
 - a. Alopecia, diarrhea, and headache
 - b. Back pain, paresthesia, and vomiting
 - c. Flushing, abdominal pain, and diarrhea
 - d. Rash, erythema, and constipation
8. In the DEFINE study, the proportion of patients experiencing a relapse within 2 years was reduced ___ with dimethyl fumarate twice daily compared with placebo.
 - a. 27%
 - b. 38%
 - c. 49%
 - d. 90%

9. In the CONFIRM study, the annualized relapse rate was reduced ___ with dimethyl fumarate twice daily compared with placebo.
- 24%
 - 29%
 - 44%
 - 51%

Case History

L.G. is a 36-year-old female recently diagnosed with MS after intermittently reporting symptoms of muscle weakness, tingling, numbness, blurred vision, and fatigue. Her current medications include a daily oral contraceptive and acetaminophen/aspirin/caffeine and rizatriptan as needed for migraines. L.G. and her physician have discussed treatment options and opted to initiate therapy with an oral agent.

10. What is the recommended initial dose of dimethyl fumarate for L.G.?
- 120 mg orally once a day
 - 120 mg orally twice a day
 - 240 mg orally once a day
 - 240 mg orally twice a day
11. After 1 week at the initial dose, what is the recommended maintenance dose of dimethyl fumarate for L.G.?
- 120 mg orally once a day
 - 120 mg orally twice a day
 - 240 mg orally once a day
 - 240 mg orally twice a day
12. Which of the following laboratory monitoring is recommended for L.G. before initiation of dimethyl fumarate therapy?
- Bilirubin
 - Complete blood count
 - Serum potassium
 - Serum transaminase
13. After taking dimethyl fumarate for a few days, L.G. calls her pharmacist for advice on how to treat the flushing she is experiencing after each dose. Her pharmacist would find which of the following recommendations to minimize flushing in the product prescribing information.
- She should be started on a lower dimethyl fumarate dose.
 - She should take dimethyl fumarate with food.
 - She should take a baby aspirin 30 minutes before each dimethyl fumarate dose.
 - She should take ibuprofen 30 minutes before each dimethyl fumarate dose.
14. Dimethyl fumarate is available as:
- An oral suspension.
 - A patch.
 - Delayed release capsules.
 - Immediate release capsules.
15. How should L.G. be instructed to store dimethyl fumarate?
- Protected from light
 - In the original container
 - At 15°C to 30°C (59°F to 86°F)
 - All of the above

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