***Cover Letter for Sample Letter of Medical Necessity***

***for a Treatment-Naïve Patient***

**The following pages may be customized to use as a letter of medical necessity for a patient**

**not previously treated with a disease-modifying therapy for relapsing multiple sclerosis.**

**Please note that the Important Safety Information does not need to be included as part of your letter.**

The following sample letter is intended to be used as a guide; therefore it is important to tailor the letter to the specific needs of your patients and address the reason(s) why VUMERITY® (diroximel fumarate) is the appropriate treatment option. You should always include pertinent clinical information that supports your decision to prescribe VUMERITY.

Please see below for considerations when writing a letter of medical necessity:

* Review the health plan’s medical policy criteria and point out the criteria that your patient meets. Explain why your patient should be excluded from any criteria that he/she/they do(es) not meet
* Provide background on your patient’s condition and clearly state your patient’s individual circumstances to justify why the prescribed therapy is the appropriate choice
* Provide clinical justification and include copies of relevant clinical data to support your decision (eg, chart notes, MRI data, etc)
* Submit the letter as required by the health plan and state guidelines. It is important that you understand the process for each health plan, including how to submit the request (fax, phone, email, the company’s website, etc) as well as how and when the decision will be communicated
* Track the status of your request and follow up with the health plan as needed

**Indication**

VUMERITY® (diroximel fumarate) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

**Important Safety Information**

**CONTRAINDICATIONS**

**VUMERITY is contraindicated in patients**

* With known hypersensitivity to diroximel fumarate, dimethyl fumarate, or to any of the excipients of VUMERITY. Reactions may include anaphylaxis and angioedema
* Taking dimethyl fumarate

**WARNINGS AND PRECAUTIONS**

**Anaphylaxis and Angioedema**

* VUMERITY can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms in patients taking dimethyl fumarate (which has the same active metabolite as VUMERITY) have included difficulty breathing, urticaria, and swelling of the throat and tongue. Patients should be instructed to discontinue VUMERITY and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema

**Progressive Multifocal Leukoencephalopathy**

* Progressive multifocal leukoencephalopathy (PML) has occurred in patients with MS treated with dimethyl fumarate (which has the same active metabolite as VUMERITY). PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. A fatal case of PML occurred in a patient who received dimethyl fumarate for 4 years while enrolled in a clinical trial

Please see Important Safety Information continued on next page and full [**Prescribing Information**](https://www.vumerityhcp.com/content/dam/commercial/vumerity/hcp/en_us/pdf/vumerity-prescribing-information.pdf).

**Progressive Multifocal Leukoencephalopathy (cont’d)**

* PML has occurred in patients taking dimethyl fumarate in the postmarketing setting in the presence of lymphopenia (<0.9 x 109/L). While the role of lymphopenia in these cases is uncertain, the PML cases have occurred predominantly in patients with lymphocyte counts <0.8×109/L persisting for more than 6 months
* At the first sign or symptom suggestive of PML, withhold VUMERITY and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes
* Magnetic resonance imaging (MRI) findings may be apparent before clinical signs or symptoms. Monitoring with MRI for signs consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present

**Herpes Zoster and Other Serious Opportunistic Infections**

* Serious cases of herpes zoster have occurred in patients treated with dimethyl fumarate (which has the same active metabolite as VUMERITY), including disseminated herpes zoster, herpes zoster ophthalmicus, herpes zoster meningoencephalitis, and herpes zoster meningomyelitis. These events may occur at any time during treatment. Monitor patients on VUMERITY for signs and symptoms of herpes zoster. If herpes zoster occurs, appropriate treatment for herpes zoster should be administered
* Other serious opportunistic infections have occurred with dimethyl fumarate, including cases of serious viral (herpes simplex virus, West Nile virus, cytomegalovirus), fungal (Candida and Aspergillus), and bacterial (Nocardia, Listeria monocytogenes, Mycobacterium tuberculosis) infections. These infections have been reported in patients with reduced absolute lymphocyte counts (ALC) as well as in patients with normal ALC. These infections have affected the brain, meninges, spinal cord, gastrointestinal tract, lungs, skin, eye, and ear. Patients with symptoms and signs consistent with any of these infections should undergo prompt diagnostic evaluation and receive appropriate treatment
* Consider withholding VUMERITY treatment in patients with herpes zoster or other serious infections until the infection has resolved

**Lymphopenia**

* VUMERITY may decrease lymphocyte counts. In the MS placebo-controlled trials with dimethyl fumarate (which has the same active metabolite as VUMERITY), mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. Four weeks after stopping dimethyl fumarate, mean lymphocyte counts increased but did not return to baseline. The incidence of infections and serious infections was similar in patients treated with dimethyl fumarate or placebo. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 x 109/L or ≤0.5 x 109/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly <0.5 x 109/L for 3.5 years)
* In controlled and uncontrolled clinical trials with dimethyl fumarate, 2% of patients experienced prolonged, severe lymphopenia (defined as lymphocyte counts <0.5 x 109/L for at least six months); in this group of patients, the majority of lymphocyte counts remained <0.5 x 109/L with continued therapy. In these patients with prolonged, severe lymphopenia, the median time for lymphocyte counts to return to normal after discontinuing dimethyl fumarate was 96.0 weeks
* In these controlled and uncontrolled clinical studies, among patients who did not experience prolonged, severe lymphopenia during treatment, the median times for lymphocyte counts to return to normal after discontinuing dimethyl fumarate were as follows:
	+ 4.3 weeks in patients with mild lymphopenia (lymphocyte count ≥0.8 x 109/L) at discontinuation,
	+ 10.0 weeks in patients with moderate lymphopenia (lymphocyte count 0.5 to <0.8 x 109/L) at discontinuation, and
	+ 16.7 weeks in patients with severe lymphopenia (lymphocyte count <0.5 x 109/L) at discontinuation.
* Neither VUMERITY nor dimethyl fumarate have been studied in patients with preexisting low lymphocyte counts

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**Lymphopenia (cont’d)**

* Obtain a complete blood count (CBC), including lymphocyte count, before initiating treatment with VUMERITY,
6 months after starting treatment, and then every 6 to 12 months thereafter, and as clinically indicated. Consider interruption of VUMERITY in patients with lymphocyte counts less than 0.5 x 109/L persisting for more than six months. Given the potential for delayed recovery of lymphocyte counts, continue to obtain lymphocyte counts until their recovery if VUMERITY is discontinued or interrupted because of lymphopenia. Consider withholding treatment from patients with serious infections until resolution

**Liver Injury**

* Clinically significant cases of liver injury have been reported in patients treated with dimethyl fumarate (which has the same active metabolite as VUMERITY) in the postmarketing setting. The onset has ranged from a few days to several months after initiation of treatment with dimethyl fumarate. Signs and symptoms of liver injury, including elevation of serum aminotransferases to greater than 5-fold the upper limit of normal and elevation of total bilirubin to greater than 2-fold the upper limit of normal have been observed. These abnormalities resolved upon treatment discontinuation. Some cases required hospitalization. None of the reported cases resulted in liver failure, liver transplant, or death. However, the combination of new serum aminotransferase elevations with increased levels of bilirubin caused by drug-induced hepatocellular injury is an important predictor of serious liver injury that may lead to acute liver failure, liver transplant, or death in some patients
* Elevations of hepatic transaminases (most no greater than 3 times the upper limit of normal) were observed during controlled trials with dimethyl fumarate
* Obtain serum aminotransferase, alkaline phosphatase (ALP), and total bilirubin levels prior to treatment with VUMERITY and during treatment as clinically indicated. Discontinue VUMERITY if clinically significant liver injury induced by VUMERITY is suspected

**Flushing**

* VUMERITY may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). In clinical trials of dimethyl fumarate (which has the same active metabolite as VUMERITY), 40% of dimethyl fumarate-treated patients experienced flushing. Flushing symptoms generally began soon after initiating dimethyl fumarate and usually improved or resolved over time. In the majority of patients who experienced flushing, it was mild or moderate in severity. Three percent (3%) of patients discontinued dimethyl fumarate for flushing and <1% had serious flushing symptoms that were not life-threatening but led to hospitalization

**Serious Gastrointestinal Reactions**

* Serious gastrointestinal (GI) reactions, including perforation, ulceration, hemorrhage, and obstruction, some with fatal outcomes, have been reported in the postmarketing setting with the use of fumaric acid esters, including VUMERITY, with or without concomitant aspirin use. The majority of these events have occurred within 6 months of fumaric acid ester treatment initiation. In controlled clinical trials, the incidence of serious gastrointestinal adverse reactions was 1% in patients treated with dimethyl fumarate; these events, none of which were fatal, included vomiting (0.3%) and abdominal pain (0.3%)
* Monitor patients, promptly evaluate, and discontinue VUMERITY for new or worsening severe gastrointestinal signs and symptoms

**ADVERSE REACTIONS**

* The most common adverse reactions (incidence ≥10% and ≥2% more than placebo) for dimethyl fumarate (which has the same active metabolite as VUMERITY) were flushing, abdominal pain, diarrhea, and nausea
* Gastrointestinal adverse reactions: Dimethyl fumarate caused GI events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). The incidence of GI events was higher early in the course of treatment (primarily in month 1) and usually decreased over time in patients treated with dimethyl fumarate compared with placebo. Four percent (4%) of patients treated with dimethyl fumarate and less than 1% of placebo patients discontinued due to gastrointestinal events. The incidence of serious GI events was 1% in patients treated with dimethyl fumarate
* Hepatic transaminases: An increased incidence of elevations of hepatic transaminases in patients treated with dimethyl fumarate was seen primarily during the first six months of treatment and most patients with elevations had levels <3 times the upper limit of normal (ULN) during controlled trials. There were no elevations in transaminases ≥3 times the ULN with concomitant elevations in total bilirubin >2 times the ULN. Discontinuations due to elevated hepatic transaminases were <1% and were similar in patients treated with dimethyl fumarate or placebo

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**ADVERSE REACTIONS (cont’d)**

* Eosinophilia adverse reactions: A transient increase in mean eosinophil counts was seen during the first 2 months of therapy

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

* There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VUMERITY during pregnancy. Encourage patients to enroll by calling 1-833-569-2635 or visiting [www.blossomspregnancyregistry.com](https://www.blossomspregnancyregistry.com/)

**Renal Impairment**

* No dosage adjustment is necessary in patients with mild renal impairment. Because of an increase in the exposure of a major metabolite, use of VUMERITY is not recommended in patients with moderate or severe renal impairment

**Please see full** [**Prescribing Information**](https://www.vumerityhcp.com/content/dam/commercial/vumerity/hcp/en_us/pdf/vumerity-prescribing-information.pdf)**.**

This sample letter is for informational purposes only, providing an example of language that may be required or helpful when responding to a request from a patient’s health plan. Use of this information does not constitute medical or legal advice and does not guarantee reimbursement for coverage. It is not intended to be a substitute for, or an influence on, the independent clinical decision of the prescribing healthcare professional.

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[Insert Date]

Request for VUMERITY® (diroximel fumarate) for My Relapsing Multiple Sclerosis (RMS) Treatment-Naïve Patient

RE: [Patient Name]

[Patient Insurance ID Number]

[Patient Date of Birth]

[Reference number]

Dear [Health Plan Contact Name]:

I am writing this letter of medical necessity in support of my request to treat [Patient Name] with
VUMERITY® (diroximel fumarate), a United States Food and Drug Administration (FDA)-approved therapy indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.1 The full prescribing information for VUMERITY can be accessed at www.vumerityhcp.com/pi.

As a board-certified [field of certification] with [XX] years of experience treating MS, I believe that the RMS medication[s] preferred by your coverage policy [is/are] not appropriate for my patient and my patient’s MS. Utilizing [name of product(s)] before VUMERITY is not appropriate for [him/her/them] because [list reason(s) medication(s) are not appropriate such as safety, efficacy, contraindications, tolerability, route of administration, etc]. [HCP to state the number of years they have been treating the patient and their opinion on the necessity of treating with VUMERITY.]

I have evaluated my patient’s clinical symptoms and have provided a summary below:

* [Date of diagnosis and ICD-10 code(s)]
* [Magnetic resonance imaging (MRI) data]
* [Physical disability, including description and related test results (eg, Expanded Disability Status Scale (EDSS) score)]
* [History of relapse(s), including dates and symptoms]
* [Pertinent laboratory values]

[HCP to insert the reasons for recommendation to use VUMERITY, which may include:]

* [Reason(s) VUMERITY is most appropriate for this patient, such as efficacy profile of this product, safety and tolerability profile of this product, pharmacokinetic profile, dosage, and/or route of administration. Please see below for a summary of some key clinical data to support the use of VUMERITY. However, please also consider including other relevant clinical data specific to your patient
	+ VUMERITY was submitted through the 505(b)(2) regulatory pathway and was approved by the FDA in October of 2019.2 It contains the same active metabolite (monomethyl fumarate [MMF]) as dimethyl fumarate (DMF). The efficacy of VUMERITY is based upon bioavailability studies comparing DMF to VUMERITY in healthy subjects and patients with RMS. The efficacy and safety of dimethyl fumarate were demonstrated in 2 randomized, double-blind, placebo-controlled studies in patients with relapsing-remitting multiple sclerosis (RRMS). In Study 1, patients were randomized to receive dimethyl fumarate 240 mg twice a day (n=410), dimethyl fumarate 240 mg three times a day (n=416), or placebo (n=408) for up to 2 years. 73% of patients taking dimethyl fumarate remained relapse-free at 2 years vs 54% with placebo (primary endpoint: 27% vs 46%; P<0.0001). 84% of patients experienced no disability progression while taking dimethyl fumarate vs 73% on placebo. In Study 2, patients were randomized to receive dimethyl fumarate 240 mg twice a day (n=359), dimethyl fumarate 240 mg three times a day (n=345), or placebo (n=350) for up to 2 years. Dimethyl fumarate demonstrated a 44% relative reduction in annualized relapse rate (ARR) vs placebo (primary endpoint: 0.224 vs 0.401; P<0.0001). The dimethyl fumarate 240 mg three times daily dose resulted in no additional benefit over the dimethyl fumarate 240 mg twice-daily dose in either study.1
	+ In clinical studies assessing safety in patients with RRMS, the adverse reaction profile of VUMERITY was consistent with the DMF clinical trials experience.1 EVOLVE-MS-2 was a phase 3, randomized, head-to-head, active-controlled study to evaluate patient-assessed gastrointestinal (GI) tolerability of VUMERITY versus DMF in patients with RRMS. Patients self-reported 46% fewer days (relative to exposure) with GI symptoms on VUMERITY versus DMF.3 Limitations and disclosures of the EVOLVE-MS-2 study include:
		- The GI symptom intensity scales are not validated
		- Results should be interpreted with caution due to the 5-week duration
		- Patients were excluded if they had a history of GI surgery, clinically significant recurring or active GI symptoms within 3 months of screening, or chronic use of medical therapy to treat GI symptoms within 1 month of screening
		- Results from this study are not included in the full Prescribing Information for VUMERITY. The FDA did not consider the results of this study when approving VUMERITY
	+ The terminal half-life of MMF is approximately 1 hour, and accumulation of MMF does not occur with multiple doses of VUMERITY.1]
* [Additional reason(s) why VUMERITY is the most appropriate treatment for this patient based on medical history and comorbidities (heart disease, hypertension, liver disease, etc), MRI data, history of relapses, or EDSS history]

I ask that you review any clinical information submitted regarding my patient when considering this request, as well as review clinical guidelines and recent clinical trial results. I have indicated the additional information submitted with this letter below:

[[ ]  Relevant medication history and/or chart notes describing previous therapies and specific outcomes

[ ]  MRI data

[ ]  Patient’s history of relapses

[ ]  EDSS history

[ ]  Supporting literature (eg, clinical guidelines, recent clinical trials, etc)]

In summary, based on the patient’s current condition and the clinical data available to date, treatment with VUMERITY for [Patient Name] is medically appropriate and necessary.

Please feel free to contact me if you require further information regarding this request. I look forward to your response as soon as possible.

Sincerely,

[Prescriber Name]

[Prescriber Specialty]

[Prescriber Contact Info]

**References**

1. VUMERITY. Prescribing Information. Cambridge, MA: Biogen.
2. Biogen. Biogen and Alkermes Announce FDA Approval of VUMERITY™ (diroximel fumarate) for Multiple Sclerosis. October 30, 2019. https://investors.biogen.com/news-releases/news-release-details/biogen-and-alkermes-announce-fda-approval-vumeritytm-diroximel. Accessed December, 18, 2023.
3. Naismith RT, Wundes A, Ziemssen T, et al. Diroximel fumarate demonstrates an improved gastrointestinal tolerability profile compared with dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: Results from the randomized, double-blind, phase III EVOLVE-MS-2 study. *CNS Drugs.* 2020;34(2):185-196.\*

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