VUMERITY® (diroximel fumarate) delayed-release capsules 231 mg

CLINICAL ATTRIBUTES

VUMERITY® (diroximel fumarate) offers the established efficacy of dimethyl fumarate[1]

In the 2-year Study 1 and Study 2 trials, dimethyl fumarate reduced key measures of disease activity and demonstrated a favorable benefit-risk profile[2-4]

Study 1 design: The trial was a 2-year, randomized, double-blind, placebo-controlled study in 1234 patients with relapsing-remitting multiple sclerosis (RRMS). Patients were randomized to either oral dimethyl fumarate 240 mg twice a day (n=410), dimethyl fumarate 240 mg 3 times a day[a] (n=416), or placebo (n=408) for up to 2 years. Neurological evaluations were performed at baseline, every 3 months, and at time of suspected relapse. Magnetic resonance imaging (MRI) evaluations were performed in a subset of patients (44%) at baseline, month 6, and years 1 and 2. The primary endpoint was the proportion of patients who relapsed (PPR). Secondary endpoints included the annualized relapse rate (ARR), time to confirmed disability progression, number of new or newly enlarging T2 hyperintense lesions, number of gadolinium-enhancing (Gd+) lesions, and the number of new T1 hypointense lesions. Key exclusion criteria included the use of interferon beta or glatiramer acetate (GA) within 3 months of randomization, use of an infusion disease-modifying therapy (DMT) within 6 months of randomization, primary progressive multiple sclerosis (MS) or secondary progressive MS, or any major disease that would preclude participation in a clinical trial. Key inclusion criteria included 1 relapse over the year preceding the trial or a brain MRI scan demonstrating at least 1 Gd+ lesion within 6 weeks of randomization and an Expanded Disability Status Scale (EDSS) score ranging from 0 to 5.[1,3]

Study 2 design: The trial was a 2-year, multicenter, randomized, double-blind, placebo-controlled study in 1417 patients with RRMS that also included an open-label comparator arm. Patients were randomized to either oral dimethyl fumarate 240 mg twice a day (n=359), dimethyl fumarate 240 mg 3 times a day[a] (n=345), an open-label comparator (n=350), or placebo (n=363) for up to 2 years. Neurological evaluations were performed at baseline, every 3 months, and at time of suspected relapse. MRI evaluations were performed in a subset of patients (48%) at baseline, month 6, and years 1 and 2. The primary endpoint was ARR. Secondary endpoints at 2 years included the PPR, time to confirmed disability progression, number of new or newly enlarging T2 hyperintense lesions, number of Gd+ lesions, and the number of T1 hypointense lesions. Key exclusion criteria included the use of interferon beta or GA within 3 months of randomization, use of an infusion DMT within 6 months of randomization, primary progressive MS or secondary progressive MS, or any major disease that would preclude participation in a clinical trial. Key inclusion criteria included 1 relapse over the year preceding the trial or a brain MRI scan demonstrating at least 1 Gd+ lesion within 6 weeks of randomization and an EDSS score ranging from 0 to 5.[1,4]

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
- PML has occurred in patients taking dimethyl fumarate in the postmarketing setting in the presence of lymphopenia ($<0.9 \times 10^9$/L). While the role of lymphopenia in these cases is uncertain, the PML cases have occurred predominantly in patients with lymphocyte counts $<0.8 \times 10^9$/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

[a]The only approved and recommended dose for dimethyl fumarate is 240 mg BID.[2]

Please see Important Safety Information continued on the following pages.

KEY CLINICAL ENDPOINTS AT 2 YEARS

Cut the risk and frequency of relapses and the risk of disability progression[1]

	Study 1	Study 2
	Placebo n=408; **dimethyl fumarate n=410**	Placebo n=363; **dimethyl fumarate n=359**
PPR[a]	Primary endpoint **49%** **Relative risk reduction** Placebo: 46% **Dimethyl fumarate: 27%** (*P*<0.0001)	**34%** **Relative risk reduction** Placebo: 41% **Dimethyl fumarate: 29%** (*P*<0.0001)
ARR[a]	**53%** **Relative reduction** Placebo: 0.364 **Dimethyl fumarate: 0.172** (*P*<0.0001)	Primary endpoint **44%** **Relative reduction** Placebo: 0.401 **Dimethyl fumarate: 0.224** (*P*<0.0001)
Disability Progression[b]	**38%** **Relative risk reduction** Placebo: 27% **Dimethyl fumarate: 16%** (*P*<0.0050)	**21%** **Relative risk reduction** Placebo: 17% **Dimethyl fumarate: 13%** **Not statistically significant (*P*=0.25)**

[a]Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.[3,4]

[b]Disability progression was defined as at least a 1-point increase from baseline EDSS of ≥1.0 (or at least a 1.5-point increase for patients with baseline EDSS of 0) sustained for 12 weeks.[1]

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Herpes Zoster and Other Serious Opportunistic Infections (cont'd)

- 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 10^9/L or ≤0.5 x 10^9/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 10^9/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 10^9/L for at least six months); in this group of patients, the majority of lymphocyte counts remained <0.5 x 10^9/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 10^9/L) at discontinuation,
  - 10.0 weeks in patients with moderate lymphopenia (lymphocyte count 0.5 to <0.8 x 10^9/L) at discontinuation, and
  - 16.7 weeks in patients with severe lymphopenia (lymphocyte count <0.5 x 10^9/L) at discontinuation.

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KEY MRI ENDPOINTS

Significantly reduced all studied measures of MRI activity[1,3-5]

	Study 1	Study 2
	Placebo n=165; **dimethyl fumarate n=152**	Placebo n=144; **dimethyl fumarate n=147**
Percentage of Subjects With No New/Newly Enlarging T2 Lesions Over 2 Years	**27%** Placebo vs **45%** **dimethyl fumarate**	**12%** Placebo vs **27%** **dimethyl fumarate**
Mean Number of New/Newly Enlarging T2 Lesions Over 2 Years	**85%** **Relative reduction** Placebo: 17.0 **Dimethyl fumarate: 2.6** (*P*<0.0001)	**71%** **Relative reduction** Placebo: 17.4 **Dimethyl fumarate: 5.1** (*P*<0.0001)
Mean Number of Gd+ Lesions at 2 Years	**90%** **Relative odds reduction** Placebo: 1.8 **Dimethyl fumarate: 0.1** (*P*<0.0001)	**74%** **Relative odds reduction** Placebo: 2.0 **Dimethyl fumarate: 0.5** (*P*<0.0001)
Mean Number of New T1 Hypointense Lesions Over 2 Years	**72%** **Relative reduction** Placebo: 5.6 **Dimethyl fumarate: 1.5** (*P*<0.0001)	**57%** **Relative reduction** Placebo: 7.0 **Dimethyl fumarate: 3.0** (*P*<0.0001)

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Lymphopenia (cont'd)

- Neither VUMERITY nor dimethyl fumarate have been studied in patients with preexisting low lymphocyte counts
- 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 10^9/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

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KEY MRI ENDPOINTS (cont'd)

Percentage of patients with Gd+ lesions at 2 years[1,6,7]

	Study 1		Study 2	
	Dimethyl fumarate n=152	Placebo n=165	Dimethyl fumarate n=147	Placebo n=144
0 lesions	**93%**	62%	**80%**	61%
1 lesion	**5%**	10%	**11%**	17%
2 lesions	**<1%**	8%	**3%**	6%
3 to 4 lesions	**0%**	9%	**3%**	2%
5 or more lesions	**<1%**	11%	**3%**	14%

Please consider referencing all clinical data, including other phase 3 studies, that support your decision to prescribe VUMERITY® (diroximel fumarate).

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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
- 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

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.

References: 1. VUMERITY. Prescribing Information. Cambridge, MA: Biogen. **2.** TECFIDERA. Prescribing Information. Cambridge, MA: Biogen. **3.** Gold R, Kappos L, Arnold DL, et al; for the DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med.* 2012;367(12):1098-1107. Published correction appears in *N Engl J Med.* 2012;367(24):2362. **4.** Fox RJ, Miller DH, Phillips JT, et al; for the CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367(12):1087-1097. Published correction appears in *N Engl J Med*. 2012;367(17):1673. **5.** Biogen, Data on file. **6.** Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis [supplementary appendix]. *N Engl J Med.* 2012;367:1098-1107. doi: 10.1056/NEJMoa1114287 **7.** Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis [supplementary appendix]. *N Engl J Med.* 2012;367(12):1087-1097. doi: 10.1056/NEJMoa1206328