PDL DRUG REVIEW

Proprietary Name: Vumerity®
Common Name: diroximel fumarate
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Tecfidera	Preferred with Conditions

Summary

Pharmacology/Usage: The mechanism by which diroximel fumarate, the active ingredient of Vumerity®, exerts its therapeutic effect in multiple sclerosis is not known. Monomethyl fumarate (MMF) is the active metabolite of diroximel fumarate, and it has been shown to activate the nuclear factor (erythroid-derived 2)- like 2 (Nrf2) pathway. The Nrf2 pathway is involved in the cellular response to oxidative stress.

After oral administration of Vumerity®, diroximel fumarate undergoes rapid pre-systemic hydrolysis by esterases and is converted to its active metabolite, monomethyl fumarate (MMF). Diroximel fumarate is not quantifiable in plasma after oral administration of Vumerity®.

Indications: 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.

There is no pregnancy category for this product; however, the risk summary indicates that there are no adequate data on the developmental risk associated with the use of Vumerity® or dimethyl fumarate (which has the same active metabolite as Vumerity®) in pregnant women. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Delayed-Release Capsules: 231mg. Swallow whole and intact; do not crush, chew or sprinkle the capsule contents on food.

Recommended Dosage: Prior to starting treatment, obtain a complete blood cell count (CBC), including lymphocyte count. Thereafter obtain a CBC, including lymphocyte count, 6 months after initiation of treatment and then every 6 to 12 months thereafter, as clinically indicated. In addition, obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to starting treatment and during treatment as clinically indicated.

Take 231mg PO BID. After 7 days, increase the dosage to the maintenance dose of 462mg PO BID. Temporary dosage reductions to 231mg BID may be considered for those who do not tolerate the maintenance dosage. Within 4 weeks, the recommended dosage of 462mg BID should be resumed. Consider discontinuation of treatment for patients unable to tolerate return to the maintenance dose.

If taken with food, avoid a high-fat, high-calorie meal/snack. The meal/snack should contain no more than 700 calories and no more than 30g of fat. In addition, avoid co-administration of Vumerity® with alcohol. Administration of non-enteric coated aspirin (up to a dose of 325mg) 30 minutes prior to Vumerity® dosing may reduce the incidence or severity of flushing.

Dose adjustments are not required with mild renal impairment; however, use is not recommended in patients with moderate or severe renal impairment. While studies have not been performed with hepatic impairment, hepatic impairment would not be expected to affect exposure and thus no dosage adjustment is needed.

Drug Interactions: Vumerity® is contraindicated in patients currently taking dimethyl fumarate, which is also metabolized to monomethyl fumarate (MMF). Vumerity® may be started the day following discontinuation of dimethyl fumarate.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (dimethyl fumarate 240mg BID) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included flushing (34%), abdominal pain (8%), diarrhea (3%), nausea (3%), vomiting (4%), pruritus (4%), rash (5%), albumin urine present (2%), erythema (4%), dyspepsia (2%), aspartate aminotransferase increased (2%), and lymphopenia (>1%).

Vumerity® may cause anaphylaxis and angioedema after the first dose or at any time during treatment. Patients should be instructed to discontinue Vumerity® and seek immediate medical care if they experience any signs and symptoms of anaphylaxis or angioedema.

Progressive multifocal leukoencephalopathy (PML) has occurred in patients with MS treated with dimethyl fumarate (which has the same active metabolite as Vumerity®). A fatal case of PML occurred in a patient who received dimethyl fumarate for 4 years while enrolled in a clinical trial. During the trial, the patient experienced prolonged lymphopenia while taking dimethyl fumarate. The patient had no other identified medical conditions resulting in compromised immune system function and was also not taking any immunosuppressive or immunomodulatory medications concomitantly. At the first sign or symptom suggestive of PML, withhold Vumerity® and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Lower PML-related mortality and morbidity have been reported after discontinuation of another MS medication associated with PML in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis. It is not known if these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

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 about 30% during the first year of treatment with dimethyl fumarate and then remained stable. Neither Vumerity® nor dimethyl fumarate have been studied in patients with pre-existing low lymphocyte counts. Obtain a CBC, including lymphocyte count, before starting treatment and as discussed in the recommended dosage section. Consider interrupting treatment in patients with lymphocyte counts $<0.5\ X10^9/L$ persisting for more than 6 months. Consider withholding treatment from patients with serious infections until resolution. Decisions on whether to restart Vumerity® or not should be individualized based on clinical circumstances.

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 post-marketing setting. The onset has ranged from a few days to several months after starting treatment with dimethyl fumarate. Signs and symptoms of liver injury, including elevations of serum aminotransferases and elevation of total bilirubin have been observed. These abnormalities resolved with treatment discontinuation. Obtain serum aminotransferases, alkaline phosphatase, and total bilirubin levels prior to treatment and during treatment as clinically indicated. Discontinue Vumerity® if clinically significant liver injury induced by Vumerity® is suspected.

Vumerity® may cause flushing. In clinical trials of dimethyl fumarate, 40% of dimethyl fumarate-treated patients experienced flushing. Flushing symptoms generally began soon after starting dimethyl fumarate and usually improved or resolved over time. In most who experienced flushing, it was mild or moderate in severity. Administering Vumerity® with food may reduce the incidence of flushing. Studies with dimethyl fumarate show that administration of non-enteric coated aspirin (up to a dose of 325mg) 30 minutes prior to dosing may reduce the incidence or severity of flushing.

Contraindications: In patients with known hypersensitivity to diroximel fumarate, dimethyl fumarate, or to any of the excipients of the product; in patients taking dimethyl fumarate

Manufacturer: Biogen Inc

Analysis: The efficacy of Vumerity® is based upon bioavailability studies in patients with relapsing forms of MS and healthy subjects comparing oral dimethyl fumarate delayed-release capsules to Vumerity® delayed-release capsules.

The clinical trials described in the Vumerity® prescribing information were conducted using dimethyl fumarate. Dimethyl fumarate, under the brand name Tecfidera®, is also metabolized to the active metabolite monomethyl fumarate (MMF). The safety and efficacy of dimethyl fumarate were assessed in 2 studies that included patients with relapsing-remitting MS (RRMS). Tecfidera® has been shown to be safe and effective in the treatment of MS, with having the same indication as Vumerity®. While there is currently no generic available for Tecfidera®, Vumerity® has the same manufacturer as Tecfidera®.

Place in Therapy: Vumerity® is indicated for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults. Vumerity® is contraindicated for use in patients currently taking dimethyl fumarate (under the brand name Tecfidera®), which has the same active metabolite as Vumerity®. The efficacy of Vumerity® is based upon bioavailability studies comparing dimethyl fumarate to Vumerity®.

The authors concluded in one phase 3 study[3] that diroximel fumarate had an improved GI tolerability profile as compared with dimethyl fumarate, as there were lower rates of gastrointestinal adverse events seen with diroximel fumarate than dimethyl fumarate. In addition, there were fewer patients who discontinued treatment with diroximel fumarate (1.6%) as compared with dimethyl fumarate (5.6%) due to adverse events and fewer who discontinued due to gastrointestinal adverse events (0.8% vs 4.8%, respectively).

There is some evidence at this time to support that Vumerity® may have better gastrointestinal tolerability as compared to dimethyl fumarate; however, there is no evidence at this time to support that Vumerity® is safer or more effective than the other currently available, more cost-effective medications. It is therefore recommended that Vumerity® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Vumerity [package insert]. Cambridge, MA: Biogen Inc; 2019.

[2] Tecfidera [package insert]. Cambridge, MA: Biogen Inc; 2019.

[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-S-2 study. *CNS Drugs*. 2020. [Epub ahead of print].