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APPLICATION NUMBER:

211855Orig1s000

SUMMARY REVIEW

Summary Memorandum for Regulatory Action

Date	October 11, 2019
From	Paul Lee, MD, PhD Nick Kozauer, MD
Subject	Summary Memorandum for Regulatory Action
NDA/BLA # and Supplement#	NDA 211855 under 505(b)(2)[1]
Applicant	Alkermes
Date of Submission	December 13, 2018
PDUFA Goal Date	October 13, 2019
Proprietary Name	Vumerity
Established or Proper Name	Diroximel fumarate
Dosage Form(s)	231 mg delayed release capsules
Applicant Proposed Indication(s)/Population(s)	VUMERITY is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis
Applicant Proposed Dosing Regimen(s)	The starting dose for VUMERITY is 231 mg twice a day orally. After 7 days, the dose should be increased to 462 mg (two 231 mg capsules) twice daily orally.
Recommendation on Regulatory Action	Tentative Approval
Recommended Indication(s)/Population(s) (if applicable)	VUMERITY is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
Recommended Dosing Regimen(s) (if applicable)	Same as proposed

[1]The referenced drug for this 505(b)(2) application is Tecfidera (NDA 204063)

1. Benefit-Risk Assessment

The application provides an adequate bridge to Tecfidera, the referenced product for this 505(b)(2) application. Therefore, the previous findings of safety and effectiveness for Tecfidera also apply to Vumerity.

2. Background

The applicant seeks approval of Vumerity (diroximel fumarate) using the 505(b)(2) regulatory pathway for monomethyl fumarate (MMF), relying on the previous findings of safety and effectiveness for Tecfidera (dimethyl fumarate [DMF]). Tecfidera is approved for the treatment of relapsing forms of multiple sclerosis. MMF is the primary and only known active metabolite of DMF. The metabolic conversion of DMF into MMF is rapid, and only MMF is detectable in serum after oral doses of DMF. Vumerity rapidly undergoes pre-systemic hydrolysis to MMF; diroximel fumarate, MMF, and metabolites of diroximel fumarate are quantifiable in plasma after administration of Vumerity.

Significant FDA communications with the applicant included a pre-IND written response (March 2014), End of Phase 2 meeting minutes (August 2015), pre-NDA meeting minutes (June 2018), and an agreement with an initial Pediatric Study Plan (November 2016).

The applicant performed ten Phase 1 studies in healthy volunteers to establish a bioequivalence bridge between Vumerity and Tecfidera, as well as to characterize its pharmacokinetic (PK) properties. In addition, the applicant has two ongoing Phase 3 safety studies in patients with relapsing forms of multiple sclerosis.

3. Product Quality

The Product Quality [Chemistry, Manufacturing, and Controls (CMC)] review team recommends approval because the applicant has adequately addressed the identified risks with the drug product, drug substance, and manufacturing.

Martha Heimann, Ph.D., is the CMC Team Lead. Please refer to Dr. Heimann's memorandum for a listing of the members of the Office of Product Quality team who reviewed this application.

A pre-approval inspection of the applicant's manufacturing facilities in 2013 had noted minor deficiencies that were resolved or clarified during the pre-approval inspection period. An inspection in 2017 of the manufacturing facility noted that the facility had a well-established manufacturing history, and the inspections did not raise significant concerns.

4. Nonclinical Pharmacology/Toxicology

The nonclinical team recommends approval.

Melissa Banks-Muckenfuss, Ph.D., performed the primary nonclinical review. Lois Freed, Ph.D., is the team leader and performed a secondary review.

The nonclinical review identified toxicity differences between diroximel fumarate and the listed drug, dimethyl fumarate (Tecfidera). Nonclinical studies identified cardiac inflammation/necrosis and physeal dysplasia in male rats that had not been noted in association with dimethyl fumarate. Stomach tumors and retinal degeneration which had been observed in nonclinical studies of dimethyl fumarate were not seen in similar studies with diroximel fumarate. The nonclinical review expressed concern that a major metabolite of diroximel fumarate, 2-hydroxyethyl succinimide (HES), which is associated with renal impairment, could be additive to the established renal toxicity of MMF. Otherwise, the nonclinical studies of diroximel fumarate identified toxicities in most of same target organs as were noted in nonclinical studies of dimethyl fumarate and confirmed that diroximel fumarate appeared to have the same embryofetal effects on survival and growth as Tecfidera.

Dr. Freed agreed with the nonclinical reviewer's overall conclusions. Dr. Freed recommends approval because of the adequacy of the nonclinical studies and advises a need for a postmarketing requirement for a juvenile animal toxicology study to support clinical development of Vumerity in the pediatric population.

5. Clinical Pharmacology

The clinical pharmacology team recommends approval because the applicant has established an adequate PK bridge to Tecfidera, which is approved for the treatment of relapsing forms of MS.

Hristina Dimova, Ph.D., performed the clinical pharmacology review. Angela Men, M.D., Ph.D., is the team leader.

The applicant performed ten Phase 1 trials with 10-104 healthy adult subjects in each trial. Study A103 is the 35-subject pivotal bioequivalence study that established the PK bridge to Tecfidera for the 462 mg dose of Vumerity. Study ALK8700-001 was the first-in-human safety trial and not included in the clinical pharmacology review.

Studies A102, A104, and A109 compared Vumerity and Tecfidera with regard to exposures of the active metabolite, MMF, in fasted and fed states with varying conditions of the fat and caloric contents of meals. Meals with increasing fat and caloric content resulted in a progressive decrease in the C_{max} of MMF. Study A104 examined the impact of a high-fat, high calorie meal on MMF concentrations and Area Under the Curve (AUC) measurements after a single dose of Vumerity or Tecfidera. The study found that the mean C_{max} for MMF was 26% lower after a single dose of Vumerity as compared to Tecfidera in the high fat, high calorie fed state. Study A109 demonstrated that while MMF parameters diminished as meal fat and calorie content increased, the AUC measurements did not differ significantly between any of the fed states. However, based on the reduction of C_{max} noted with high-fat, high-calorie meals, and the lack of a clinically meaningful food effect otherwise, the clinical pharmacology team agrees with the applicant's labeling language instructing patients to take Vumerity "(b) (4) avoid a high-fat, high-calorie meal."

Study A106 was an adequate alcohol effect study that demonstrated a 40% decrease in C_{max} with alcohol ingestion and led to the clinical pharmacology team's recommendation of avoiding alcohol ingestion with administration of Vumerity.

Study A107 was an adequate drug-drug interaction study that demonstrated no effect of digoxin exposure on the PK profile of Vumerity.

Study A105 was an adequate mass balance study that identified a major metabolite of diroximel fumarate, HES, that is excreted in urine. Study A108 was a renal impairment study to examine the impact of renal function on the PK of MMF and HES after a single dose of Vumerity. Renal clearance of MMF decreased in the moderate and severe renal impairment groups. The AUC of HES increased with increasing renal impairment. The clinical pharmacology team therefore recommends that a dose adjustment of Vumerity is not necessary in patients with mild renal impairment, and that Vumerity should not be recommended for patients with moderate and severe renal impairment.

Study A110 was a thorough QT study that demonstrated no effect on QT intervals following multiple doses of Vumerity.

In the pivotal bioequivalence study (A103), as demonstrated in Figure 1 and Table 1, Vumerity met the criteria for bioequivalence to Tecfidera with regard to the exposure of MMF (both C_{max} and AUC), when administered in the fasted state.

Figure 1: Applicant Figure, MMF Plasma Concentration after Administration of Vumerity and Tecfidera (Study A103)

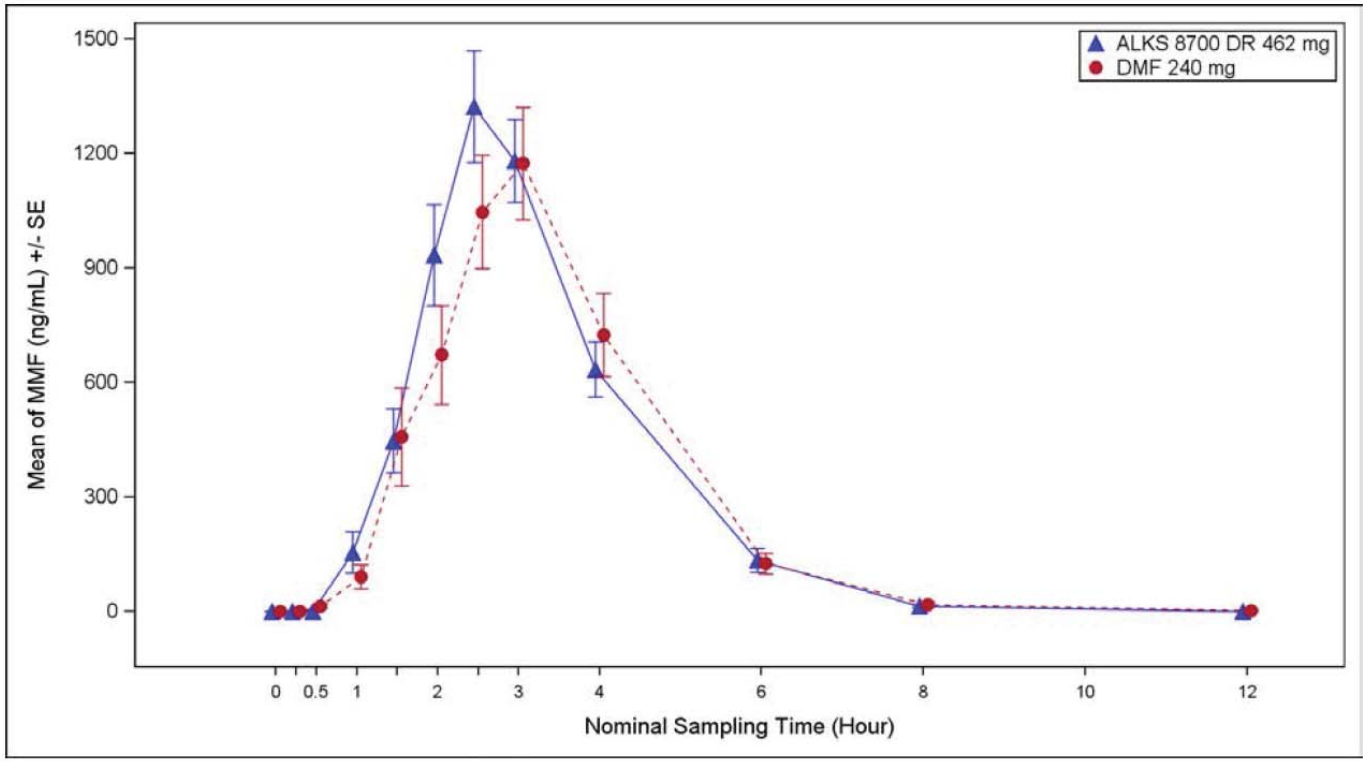

Table 1: Reviewer Table, Summary of Bioequivalence Parameters

Parameter	Vumerity	Tecfidera	Geometric Mean Ratio	90% Confidence Interval
C_{max} (μg/ml)	1.57 ± 0.07	1.67 ± 0.07	0.94	0.82-1.07
AUC_{last} (μg·hr/ml)	3.38 ± 0.05	3.14 ± 0.05	1.08	1.00-1.16
AUC_{∞} (μg·hr/ml)	3.57 ± 0.06	3.56 ± 0.07	1.00	0.88-1.14

Source: Clinical pharmacology reviewer

The applicant has submitted adequate information to support approval, based upon an established pharmacokinetic bridge to Tecfidera, which is an approved product that, like Vumerity, is a prodrug for monomethyl fumarate.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The application contains no new efficacy information for review. Because of the adequately established PK bridge to Tecfidera, substantial evidence of effectiveness is provided by reference to the approved labeling for Tecfidera.

8. Safety

David Jones, M.D., reviewed the safety data provided in this application. He recommends approval because the types of adverse events and the rates of these events in the development program for Vumerity are similar to those described in the approved labeling for Tecfidera. In addition, the applicant provided an adequate PK bridge to the Tecfidera NDA; so, the safety findings with Tecfidera are also applicable to Vumerity.

The safety population for this application includes 467 healthy adult subjects, including those otherwise healthy with renal impairment, who participated in the ten Phase 1 trials undertaken by the applicant. Additionally, there are 696 patients with relapsing forms of multiple sclerosis enrolled in a long-term, open-label safety and tolerability trial of Vumerity, and 187 patients enrolled in a double-blind study comparing gastrointestinal tolerance of Vumerity and Tecfidera. The final safety findings from these ongoing enrolled trials were not available for review, but the applicant shared preliminary safety data from these trials in the application. The application also refers to the safety data from patients in controlled trials of Tecfidera described in the Tecfidera labeling. Table 2 is adapted from Dr. Jones's review and summarizes the human exposure data for Vumerity.

Table 2: Reviewer Table, Description of Clinical Studies of Vumerity

Trial Identity	**Trial Design**	**Regimen**	**Study Endpoints**	**Treatment Duration / Follow Up**	**No. of subjects enrolled**	**Study Population**	**No. of Centers (and Countries)**
Studies to Support Safety							
ALK8700-001	First in human, single-ascending dose; single-dose, 2-treatment, 2-period crossover; single dose, 4 treatment, 4-period crossover	Single dose of diroximel fumarate 49, 105, 210, 430, 630, 840, or 980 mg *or* Tecfidera 240 mg	PK, safety and tolerability of diroximel fumarate compared to Tecfidera	Single dose on day 9 *or* days 1 and 8 *or* days 1, 8, 15, and 22	104 total 78 (diroximel fumarate & Tecfidera) 26 (placebo)	Healthy adults	1
ALK8700-A102	Food effect (Part A) and multiple ascending dose (Part B)	Single dose of 420 mg diroximel fumarate *or* diroximel fumarate 210, 430, or 630 mg twice daily	PK, safety and tolerability of diroximel fumarate	Single dose diroximel fumarate on days 1 and 4, *o*r twice daily diroximel fumarate on days 1-5	76 total all diroximel fumarate	Healthy adults	1
ALK8700-A103	Fasted relative bioavailability (Pivotal bioequivalence study)	Vumerity 426 mg *or* Tecfidera 240 mg	PK, safety, and tolerability of Vumerity vs Tecfidera	Single dose of Vumerity *or* Tecfidera days 1 and 8	35 All received Vumerity and Tecfidera	Healthy adults	1
ALK8700-A104	Relative bioavailability after a high-fat meal	Vumerity 462 mg *or* Tecfidera 240 mg	Bioavailability, PK, safety, and tolerability of Vumerity vs Tecfidera	Single dose of Vumerity *or* Tecfidera on days 1 and 3	42 All received Vumerity and Tecfidera	Healthy adults	1

ALK8700-A105	Mass balance study	Single dose of unlabeled and labelled diroximel fumarate 462 mg	PK of labelled [^{14}C]-diroximel fumarate and its metabolites	Single dose of diroximel fumarate on days 1 and 8	10 All received Vumerity	Healthy adult males	1
ALK8700-A106	Effect of alcohol study	Vumerity 462 mg	Extrinsic Factor (alcohol) PK	Single dose of Vumerity on days 1,8, and 15	31 All received Vumerity	Healthy adults	1
ALK8700-A107	Drug interaction study	Vumerity 462 mg; digoxin 0.25 mg	Extrinsic Factor (digoxin) PK	Digoxin on Day 1, digoxin and twice daily Vumerity on day 11, twice daily Vumerity on days 12-15	24 All received Vumerity	Healthy adults	1
ALK8700-A108	Renal impairment study	Vumerity 462 mg	Intrinsic Factor (renal impairment) PK	Single dose of Vumerity on day 1	32 All received Vumerity	Healthy adult subjects and those with renal impairment	3 (1)
ALK8700-A109	Relative bioavailability after a low / medium-fat meal	Vumerity 462 mg *or* Tecfidera 240 mg	Bioavailability, PK, safety, and tolerability of Vumerity vs Tecfidera	Single dose of Vumerity *or* Tecfidera on days 1, 4, 7, and 10	48 All received Vumerity and Tecfidera	Healthy adults	1
ALK8700-A110	Thorough QT study	Vumerity 462 *or* 924 mg, moxifloxacin 400 mg, and matching placebo	EKG / QTcF effects, safety, and tolerability of Vumerity	Twice daily Vumerity (or placebo) on days 2-5 and 7-10. Single dose Vumerity on days 6 and 11. Moxifloxacin (or	65 All received Vumerity	Healthy adults	1

				placebo) on days 1 and 12.			
ALK8700-A301	Long-term, open-label study	Vumerity 462 mg[b]	Long term safety and tolerability of Vumerity	Twice daily Vumerity for up to 96 weeks	696[a] All received Vumerity	Relapsing MS	103 (10)
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
ALK8700-A302	Double-blind study of gastrointestinal tolerance with Vumerity vs. Tecfidera	Vumerity 462 mg[b] *or* Tecfidera 240 mg twice daily	To compare gastrointestinal tolerance of Vumerity vs Tecfidera using 2 scales[c]	Twice daily Tecfidera *or* Vumerity for 5-weeks	187[a] 1:1 randomization Vumerity or Tecfidera	Relapsing MS	65 (2)

a As of 120-day update to application
b Begin 231 mg twice daily x 1 week, then titrate to 462 mg twice daily
c Individual GI Symptom and Impact Scale (IGISIS) and the Global GI Symptom and Impact Scale (GGISIS) scales

There were no deaths and no serious adverse events in any of the ten Phase 1 trials. One subject administered Tecfidera discontinued Study A109 because of a rash, and one subject each who was administered Vumerity withdrew from Studies A102, A106, A107, and A110 because of ventricular extrasystole, elevated creatine kinase secondary to excessive exercise, toothache, and a hypersensitivity reaction, respectively.

The reported frequency of adverse events in healthy volunteers in Phase 1 studies' receiving Vumerity was approximately 85% and for subjects receiving Tecfidera was 90%. As demonstrated in the table below summarizing all adverse events from Phase 1 trials in which subjects received Vumerity 462 mg and Tecfidera 240 mg, the most common adverse event reported with either Vumerity or Tecfidera was flushing. In a comprehensive review of the adverse events by trial and collectively performed by Dr. Jones, the most common adverse events other than flushing were from the gastrointestinal disorders system organ class, and the pattern of treatment-associated mild adverse events overall was consistent with what is expected with Tecfidera.

Table 3: Reviewer Table, All Adverse Events, Studies A103, A104, and A109

Adverse Event[1] (Preferred Term)	**Vumerity 462 mg (N=101)**	**Tecfidera 240 mg (N=101)**
Flushing	59	63
Dizziness	3	4
Nausea	2	3
Abdominal distension	1	1
Abdominal pain/discomfort	1	3
Constipation	2	0
Diarrhea	0	2
Headache	6	9
Rash	0	2

[1] Adverse events in this table represent total number of reported events. A single patient may have experienced more than one event represented in this table.

The application contained preliminary safety data from the longest exposed cohort in the ongoing safety study (A301) and a gastrointestinal tolerability study comparing Vumerity to Tecfidera. These trials' populations, patients with relapsing forms of multiple sclerosis, are the proposed indicated population for Vumerity. Therefore, the patients in Studies A301 and A302 represent the most appropriate population available from which to generalize safety conclusions. As indicated in the table below, on average, there has been approximately one year of cumulative exposure to the 462 mg dose of Vumerity in Study A301, the longest ongoing clinical trial in patients with multiple sclerosis.

Table 4: Reported Exposure in Longest Ongoing Clinical Trial in MS (Study A301)

Duration in Study (Days)	
Mean ± SD	359.4 ± 167.0
Median	419
Min, max	1,692

As of the 120-day update to the application, there had been four deaths in Study A301. The causes of death were accidental fall, hypertensive cardiac disease, cardiac arrest, and bilateral bacterial pneumonia. The applicant stated that the four deaths were not related to Vumerity treatment. Dr. Jones conjectures that the death due to extensive pneumonia could be attributable to Vumerity despite the applicant's statement that a normal range total lymphocyte count was obtained in the patient prior to death because there can be selective reductions in lymphocyte subpopulations associated with fumarate esters that may confer a risk of a serious infection even in the setting of a "normal" total lymphocyte count. However, no clear association with Vumerity has been established. There have been 47 patients who discontinued the trial due to adverse events, the most common (n=7, 1%) reported event being "multiple sclerosis relapse" which occurs in patients with relapsing forms of multiple sclerosis and is not considered a treatment-related event.

The applicant reported 72 serious adverse events occurring in 52 patients in Study A301. A review of these events revealed that 48.6% (35/72) were coded as "multiple sclerosis relapse" and are "serious" by definition because of standard of care in many countries requiring hospitalization for a clinical relapse. The remaining serious adverse events occurring more than once were a known side effect of fumarate esters (flushing, n=2), were deemed unlikely to be related to Vumerity (respiratory failure, n=2), or were sequelae of multiple sclerosis (depression/suicidal ideation and eighth cranial nerve injury, n=2 each.) The remaining serious adverse events were single isolated occurrences that are difficult to contextualize in an open-label trial, and, as reviewed by Dr. Jones, do not raise concerns of any new safety signals with Vumerity.

The applicant reports that 83.1% of patients in Study A301 have reported at least one adverse event. As demonstrated in the following table which collapses multiple reports of the same adverse event for the same patient and groups similar

adverse events, the most common adverse events, experienced by 44% of patients with multiple sclerosis taking Vumerity, are flushing and related phenomena. Infections occurred in 43% of patients and are common findings in any clinical trial and are not unexpected in association with a treatment that causes a reduction in circulating lymphocytes. The treatment emergent adverse events reported to date in Study A301 reveal no new or concerning safety issues not already known and represented in Tecfidera's approved labeling.

Table 5: Reviewer Table, Office of New Drugs 1 Analysis of Adverse Events in Study A301

Adverse Event Preferred Terms	**N (%)**
Flushing, feeling hot, erythema, generalized erythema[1]	305 (44%)
Infection (all)	297 (43%)
Upper respiratory infection, cold, rhinitis, upper respiratory tract infection, flu-like illness	211 (30%)
Multiple sclerosis relapse, multiple sclerosis	112 (16%)
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-difficile	92 (13%)
Abdominal pain, distension, bloating, spasm, irritable bowel syndrome, megacolon	87 (13%)
dyspepsia, nausea, vomiting, indigestion, epigastric pain, gastritis, duodenal symptoms	70 (10%)
Asthenia, fatigue, malaise, weakness, narcolepsy	69 (10%)
Pruritis	64 (9%)
Viral infection (all)	63 (9%)
Headache	61 (9%)
Urinary tract infection	60 (9%)
Leukopenia (neutropenia and/or lymphopenia)	60 (9%)
Nausea, vomiting	60 (9%)
Fall, dizziness, balance disorder	58 (8%)
Fall, dizziness, balance disorder, gait disturbance, difficulty walking	58 (8%)
Somnolence, fatigue, sedation	53 (8%)
Lymphopenia	49 (7%)

Elevated liver transaminases	42 (6%)
Arthralgia, arthritis, arthrosis	39 (6%)
Bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	33 (5%)

[1] Queries added to this tool for MS relapses and flushing

Source: Clinical reviewer's analysis

The applicant submitted data reflecting safety findings in patients from the initial phase (Part A) of Study A302, a planned two-part gastrointestinal tolerability. There have been no deaths in Part A of Study A302. There have been three serious adverse events (two multiple sclerosis relapses, one atrial fibrillation unrelated to Vumerity treatment). As indicated in the following table, the most commonly reported treatment-emergent adverse event in patients with either treatment was flushing, and there were no meaningful differences between adverse event rates for the two treatments in this small patient population.

Table 6: Reviewer Table, Office of New Drugs 1 Analysis of Adverse Events in Study A302 Part A

Adverse Event Preferred Term	**Vumerity 462 mg n=59**	**Tecfidera 240mg n=59**
Flushing, feeling hot, erythema, generalized erythema[1]	28 (47%)	33 (56%)
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-difficile	14 (23.7%)	12 (20.3%)
Dyspepsia, nausea, vomiting, indigestion, epigastric pain, gastritis, duodenal symptoms	14 (23.7%)	11 (18.6%)
Nausea, vomiting	14 (23.7%)	11 (18.6%)
Infections (all)	14 (23.7%)	9 (15.3%)
Abdominal pain, distension, bloating, spasm, IBS, megacolon	12 (20.3%)	14 (23.7%)
URI, cold, rhinitis, upper respiratory tract infection, flu-like illness	9 (15.3%)	4 (6.8%)
Asthenia, fatigue, malaise, weakness, narcolepsy	4 (6.8%)	7 (11.9%)
Pruritis	4 (6.8%)	6 (10.2%)

Urinary tract infection	4 (6.8%)	4 (6.8%)
Somnolence, fatigue, sedation	4 (6.8%)	4 (6.8%)
Elevated liver transaminases	2 (3.4%)	3 (5.1%)
Multiple sclerosis, multiple sclerosis relapse	2 (3.4%)	2 (3.4%)
Fever, rigors	2 (3.4%)	1 (1.7%)
Rash, eruption, dermatitis	2 (3.4%)	1 (1.7%)
Paresthesia, hypoaesthesia	2 (3.4%)	1 (1.7%)
Nephrosis, proteinuria, nephropathy	2 (3.4%)	1 (1.7%)
Pneumonia	2 (3.4%)	(0%)
Constipation	2 (3.4%)	(0%)
Headache	1 (1.7%)	6 (10.2%)
Viral Infection (all)	14 (23.7%)	12 (20.3%)

[1] Queries added to this tool for MS relapses and flushing

Source: Clinical reviewer's analysis

The safety data submitted with this application are consistent with the known safety profile of Tecfidera and support approval.

9. Advisory Committee Meeting

There was no advisory committee for this 505(b)(2) application because efficacy has been established through bioequivalence with the listed drug, Tecfidera, the clinical trials were acceptable, the safety findings were clear, and the safety profile was similar to the listed drug.

10. Pediatrics

No clinical pediatric data are provided. An initial Pediatric Study Plan proposed by the applicant was found acceptable.

11. Other Relevant Regulatory Issues

The listed product upon which this application relies is subject to a period of patent and/or exclusivity protection until October 20, 2019. Therefore, a final approval of this application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the patent and/or exclusivity period has expired.

12. Labeling

The labeling for Vumerity will largely rely on the approved Tecfidera labeling. There will be a recommendation of avoidance of use of Vumerity in patients with moderate and severe renal failure that differs from the Tecfidera labeling. There will also be recommendations to not take Vumerity with alcohol or high-fat/high-calorie meals. There are no outstanding labeling issues.

13. Postmarketing Recommendations

Pediatric studies and a pregnancy registry will be requested as postmarketing requirements.

14. Recommended Comments to the Applicant

None.

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/s/

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