CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211855Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 211855
Review 1

Drug Product Name	Vumerity™ (diroximel fumarate)
Dosage Form	Delayed-release capsules
Strength	231 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Alkermes, Inc.
US agent, if applicable	

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Haripada Sarker	Haripada Sarker
Drug Product	Rao Kambhampati	Wendy Wilson-Lee
Manufacturing	Yuesheng Ye	Yaodong (Tony) Huang
Microbiology	N/A	N/A
Biopharmaceutics	Mei Ou	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s) Reviewed	Document Date	Discipline(s) Affected
SD-001, Original NDA	12/13/2018	All
SD-009, Response to IR	6/17/2019	Biopharmaceutics
SD-010, Response to IR [1]	7/12/2019	Manufacturing
SD-014, Container closure labels	8/16/2019	Drug Product/Labeling

[1] Submission of updated CMC sections following discussions during PAI

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II	(b) (4)	Diroximel fumarate	Adequate	8/23/2019	Reviewed by H. Sarker
	IV		HDPE capsule	N/A [1]		
	III		HDPE bottles	N/A [1]		
	III		CR closure	N/A [1]		

[1] Adequate information provided in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
NDA	204063	Tecfidera(R) (dimethyl fumarate) delayed-release capsules, NDA referenced under 505(b)(2) to support safety and efficacy of diroximel fumarate.
IND	120446	Development of diroximel fumarate

2. CONSULTS

None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends **Approval** of NDA 211855 for Vumerity (diroximel fumarate) delayed-release capsules. The application, as amended in response to Agency information requests (IRs), provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Alkermes has developed Vumerity (diroximel fumarate) as a novel ester prodrug for monomethyl fumarate (MMF). MMF is the active metabolite of dimethyl fumarate, which is marketed under NDA 204063 by Biogen, asTecfidera® (dimethyl fumarate) delayed-release capsules 120 mg and 240 mg, for treatment of multiple sclerosis (MS).

In this 505(b)(2) NDA, Alkermes proposes marketing of diroximel fumarate as 231 mg delayed-release capsules for treatment of MS. The applicant indicates that, after oral administration, diroximel fumarate undergoes rapid, presystemic hydrolysis to produce MMF as the major active metabolite. The applicant also indicates that, under fasted conditions, a 462 mg dose of diroximel fumarate (two delayed-release capsules) provides MMF exposure comparable to that of 240 mg Tecfidera. The applicant relies on pharmacokinetic between Vumerity and Tecfidera, and clinical safety studies, to support approval.

Proposed indication(s) including intended patient population	Treatment of patients with relapsing forms of multiple sclerosis.
Duration of treatment	Chronic
Maximum daily dose	924 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: **Adequate**

Diroximel fumarate is a well-characterized small molecule that is manufactured for the applicant by (b) (4) Information regarding manufacture and control of the bulk drug substance is incorporated by

cross-reference to the manufacturer's DMF (b) (4) The DMF was reviewed and is deemed adequate to support approval of the NDA. Summary information submitted directly to the NDA, including general properties, characterization, specification and analytical procedures, and stability, is consistent with the information in the DMF. Drug substance impurities that exceed the ICH Q3A qualification threshold (0.15%) were adequately qualified in nonclinical studies

Drug Product: **Adequate**

(b) (4)

Manufacturing: **Adequate**

(b) (4)

All facilities involved in the manufacture and testing of Diroximel fumarate USP and Vumerity (diroximel fumarate) delayed release capsules are currently acceptable.

Biopharmaceutics: **Adequate**

The in vitro dissolution method has acceptable discriminating ability with respect to critical process parameters (e.g., (b) (4) (b) (4) , material attributes (e.g., (b) (4) , formulation changes (e.g., (b) (4)), and changes in stability storage

conditions. The dissolution method is suitable as a quality control test for the proposed delayed release drug product and the proposed acceptance criteria are acceptable.

(b) (4)

Labeling: **Adequate**

The proposed labeling is generally deemed adequate. Minor deficiencies related to listing of excipients and manufacturer will be corrected during labeling revisions.

Environmental: **Adequate**

The applicant submitted a claim for categorical exclusion under 21 CFR §25.31(b). Approval of the application would increase use diroximel fumarate and its active metabolite, MMF. However, the estimated concentration of the substance at the point of entry into the aquatic environment, (b) (4) parts per billion (ppb) is below the 1 ppb threshold and no extraordinary circumstances exist. The claim for categorical exclusion is granted.

Methods Verification:

Verification of analytical procedures submitted in the NDA by FDA laboratories was not requested during the review.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay, stability	Formulation, container closure, moisture, process parameters	L	(b) (4)	Adequate	
Content uniformity	Formulation, raw materials, process parameters, scale/equipment/site	L		Adequate	
Physical stability (b) (4)	Formulation, raw materials, process parameters, scale/equipment/site	L		Adequate	
Microbial limits	Formulation, raw materials, process parameters, moisture, container closure	L		Adequate	
Alcohol dose dumping	Formulation, raw materials, process parameters, scale/equipment/site	L		---	Impact of alcohol evaluated in *in-vivo* studies reviewed by Office of Clinical Pharmacology
Dissolution	Formulation, raw materials (b) (4) source, API sources, process parameters, scale/equipment/site	L		Adequate	

D. List of Deficiencies for Complete Response: Not applicable.

Application Technical Lead Name and Date: See signature page.

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LABELING

NDA 211855

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Vumerity™ (diroximel fumarate) delayed-release capsules
Dosage form, route of administration	Capsule, Oral
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Delayed-release capsules: 231 mg

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Yes. VUMERITY should not be crushed or chewed and the capsule contents should not be sprinkled on food.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Yes. VUMERITY is available as hard, hydroxypropyl methylcellulose, delayed-release capsules containing 231 mg of diroximel fumarate. The capsules have a white cap and a white body, printed with "DRF 231 mg" in black ink on the body.
Strengths: in metric system	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not applicable
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	No
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	No

5. *Section 16 How Supplied/Storage and Handling*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes but needs to be changed.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: ***Adequate after the following changes are made:***

(b) (4)

The Prescribing Information complies with all regulatory requirements from a CMC perspective after the above changes are made.

II. Labels:

1. ***Container Labels***

(b) (4)

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes	Yes
Dosage strength	Yes	Yes
Net contents	Yes	Yes
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Yes	Yes but needs to be edited
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available		

Reviewer's Assessment of Labels: ***Adequate after the following changes are made:***

On all container and carton labels, the storage statement should be changed from (b) (4) **to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)** (b) (4) (b) (4) **If there is a space limitation, reference to** (b) (4) **may be removed.**

The labels comply with all regulatory requirements from a CMC perspective after the above changes are made.

List of Deficiencies:

1) **In the Description section of the prescribing information document, include the following:**
   - (b) (4)
   - **The inactive ingredients should be listed in an alphabetical order.**

2) On all container and carton labels and in the How Supplied section of the Prescribing Information, the storage statement should be changed from (b) (4) to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (b) (4) (b) (4) (b) (4) If there is a space limitation, reference to may be removed.

Overall Assessment and Recommendation: Recommended for Approval after above deficiencies are fulfilled

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 8/11/19

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Rao Kambhampati

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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 8/14/2019 08:34:47AM
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BIOPHARMACEUTICS

NDA: 211855 [505(b)(2)]
Drug Product Name / Strength: VUMERITY™ (diroximel fumarate) delayed-release capsules, 231 mg
Proposed Indication: For the treatment of patients with relapsing forms of multiple sclerosis
Route of Administration: Oral
Applicant Name: Alkermes, Inc.
Submission Dates:
12/13/2018 (Original submission)
06/17/2019 (Response to Biopharmaceutics Information Request)
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

EXECUTIVE SUMMARY

The proposed VUMERITY™ (diroximel fumarate) delayed-release capsules (231 mg) is a solid oral dosage drug product that contains delayed release (DR) (b) (4) (b) (4) Each (b) (4) contains (b) (4) of the drug substance diroximel fumarate, and (b) (4) are encapsulated within a white, two-piece, hydroxypropyl methylcellulose (HPMC) capsule shell to achieve 231 mg strength. The listed drug (LD) product of this 505(b)(2) application is Tecfidera® (dimethyl fumarate) delayed-release capsules, 120 mg and 240 mg (approved under NDA 204063 on 03/27/2013).

In the current submission, the Biopharmaceutics review focused on the evaluation of i) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product for batch release and stability test, and ii) the need of in vitro bridge studies.

In Vitro Dissolution Testing of the Finished Product:

(b) (4)

The approved *in vitro* dissolution method and acceptance criteria for the proposed drug product are as follows:

USP Apparatus	II (paddle) with custom sinker
Rotation Speed	75 rpm
Dissolution Media	Acid Stage (for 2 hours): 750 mL of 0.1 M HCl Buffer Stage (for 1 hour): 745 mL of 0.1 M HCl and 200 mL of 0.2 M tribasic sodium phosphate buffer to obtain a pH of 6.5 ± 0.10 buffer, 945 mL in total
Temperature	37°C±0.5°C
Acceptance Criteria	Acid Stage: NMT (b) (4) in 2 hours Buffer Stage: Q= (b) (4) in 60 minutes

In Vitro Bridging:

(b) (4)

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 211855 for the proposed VUMERITY™ (diroximel fumarate) delayed-release capsules, 231 mg, is recommended for **APPROVAL**.

BIOPHARMACEUTICS REVIEW

1. In Vitro Dissolution Method

The detailed recommendation regarding the dissolution method development and selection of dissolution acceptance criteria was conveyed to the Applicant in (i) the meeting minutes for a Type B (End-of-Phase 2) meeting, dated 09/04/2015, and (ii) the written response for Type C CMC only, dated 03/10/2016, cross-referenced to IND 120446. Following the FDA's recommendation, the Applicant submitted the completed dissolution method development report (702-07642) in M.3.2.P.5.6 in support of the NDA.

Per the Applicant, upon oral ingestion, the HPMC capsule shell of the proposed drug

(b) (4)

Mei Ou

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Ta-Chen Wu

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTHA R HEIMANN
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