CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211855Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	October 31, 2019
Reviewer:	Sara Karami, Ph.D., M.P.H Division of Epidemiology I
Team Leader:	Kira Leishear, Ph.D., M.S. Division of Epidemiology I
Deputy Division Director:	CAPT Sukhminder K. Sandhu, Ph.D., M.S., M.P.H. Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Vumerity™ (diroximel fumarate)
Application Type/Number:	NDA 211855
Applicant/sponsor:	Alkermes, Inc.
OSE RCM #:	2019-2149

1. BACKGROUND INFORMATION

1.1. Medical Product

Diroximel fumarate (Vumerity™) is a delayed-release medication for the treatment of relapsing forms of multiple sclerosis (RMS) in adults. After oral administration, diroximel fumarate is presystemically hydrolyzed by intestinal esterases into monomethyl fumarate (MMF) and 2-hyroxyethyl succinimide (HES), a major inactive metabolite. Subsequently, both MMF and HES are absorbed by the small intestine.

While the exact therapeutic mechanism of diroximel fumarate on RMS is unknown, MMF is the primary and only known active metabolite of dimethyl fumarate (DMF, Tecfidera), which was approved for RMS treatment in 2013. Because diroximel fumarate is not quantifiable in plasma, the clinical effects, safety, pharmacokinetic and pharmacodynamic evaluations of diroximel fumarate are performed using MMF plasma concentrations. The terminal half-life of MMF is about one hour.[1] Accumulation of MMF does not occur with multiple doses of diroximel fumarate and in the majority of individuals no circulating MMF is present within 24-hours.[1] MMF is shown to activate the nuclear factor (erythroid-derived 2)-related factor 2 (NrF2) antioxidant response pathway, which is involved in the cellular response to oxidative stress.

Given the adequate pharmacologic bridge between diroximel fumarate and DMF, this application utilizes the 505(b)(2) regulatory pathway, relying on DMF as the reference product.

Vumerity™, a delayed-release hard capsule for oral use, contains 231mg of diroximel fumarate. According to the labeling, the medication's starting dose is 231mg twice a day for seven days; the maintenance dose, following the initial seven days, is 462mg twice a day. The "DOSAGE AND ADMINISTRATION" section for Vumerity™ states:[1]

- Blood tests are required prior to initiation of VUMERITY (2.1)
- Starting dose: 231 mg twice a day, orally, for 7 days (2.2)
- Maintenance dose after 7 days: 462 mg (administered as two 231 mg capsules) twice a day, orally (2.2)
- Swallow VUMERITY capsules whole and intact. Do not crush, chew, or sprinkle capsule contents on food (2.3)
- Avoid administration of VUMERITY with a high-fat, high-calorie meal/snack (2.3)
- Avoid co-administration of VUMERITY with alcohol (2.3)

Warnings and precautions for Vumerity™ include anaphylaxis and angioedema, progressive multifocal leukoencephalopathy, lymphopenia, liver injury, and flushing. Specifically, the "WARNING AND PRECAUTIONS" section for Vumerity™ states:[1]

- Anaphylaxis and Angioedema: Discontinue and do not restart VUMERITY if these occur. (5.1)
- Progressive Multifocal Leukoencephalopathy (PML): Withhold VUMERITY at the first sign or symptom suggestive of PML. (5.2)

- Lymphopenia: Obtain a CBC including lymphocyte count before initiating VUMERITY, after 6 months, and every 6 to 12 months thereafter. Consider interruption of VUMERITY if lymphocyte counts <0.5 × 109/L persist for more than six months. (5.3)
- Liver Injury: Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiating VUMERITY and during treatment, as clinically indicated. Discontinue VUMERITY if clinically significant liver injury induced by VUMERITY is suspected. (5.4)

Table 1 shows all adverse reactions reported for dimethyl fumarate at ≥2% higher incidence compared to the placebo. The most common adverse reactions (≥10% in patients treated with DMF 240mg twice a day and ≥2% more than placebo) described for diroximel fumarate include: flushing, abdominal pain, diarrhea and nausea. There are no Risk Evaluation and Mitigation Strategies (REMS) planned for diroximel fumarate in adult patients with RMS.[2]

Table 1: Adverse Reactions Reported for Dimethyl Fumarate at ≥2% Higher Incidence than Placebo		
Adverse Reactions	Dimethyl Fumarate 240 mg Twice Daily (N=769) %	Placebo (N=771) %
Flushing	40	6
Abdominal pain	18	10
Diarrhea	14	11
Nausea	12	9
Vomiting	9	5
Pruritus	8	4
Rash	8	3
Albumin urine present	6	4
Erythema	5	1
Dyspepsia	5	3
Aspartate aminotransferase increased	4	2
Lymphopenia	2	<1
Source: Reference 2		

1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the United States (U.S.) general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[3] The potential risk/benefit profile of MS disease-modifying treatment during pregnancy is unclear; pregnancy may reduce the risk of MS relapse, but there may be an increased risk of relapse after delivery or when stopping MS treatment.[4]

According to the label, there are no adequate data on the developmental risk associated with the use of diroximel fumarate or DMF in pregnant women.[1] In animal studies of rats and rabbits, administration of diroximel fumarate during pregnancy resulted in adverse effects on embryofetal and offspring development; fetal skeletal abnormalities, increased fetal mortality, and decreased fetal body weight were reported at the highest doses tested, which were associated with maternal toxicity and were at similar, to two-fold higher (MMF), than the recommended human dose.[1]

According to the label, there are no adequate data on the presence of diroximel fumarate or metabolites (MMF, HES) in human milk.[1] The effects on the breastfed infant and on milk production are unknown. In animal studies, oral administration of diroximel fumarate to rats throughout gestation and lactation resulted in adverse effects on the offspring where reduced body weight, persisting into adulthood, and neurobehavioral impairment were reported at the highest doses tested; dosing was approximately three-fold higher (MMF) than the recommended human dose.[1]

Per the clinical review, there have been ten completed Phase 1 studies (6 with DRF, 4 with DRF or DMF) and two Phase 3 trials were ongoing (1 with DRF, 1 with DRF or DMF) . These studies withdrew participants in the setting of pregnancy. Individuals were also excluded from participating if they "were pregnant or breastfeeding or planned to become pregnant or began breastfeeding at any point during the study and for 30 days after any study drug administration."[1] Additionally, sexually-active female participants of childbearing potential were to agree to the use of two methods of contraception during the study and for 30 days after the final study drug administration.[1]

As of November 30, 2018, eight pregnancies (one from a Phase 1 study and seven from a Phase 3 trial) have been reported. Of the pregnancies identified during the on-going Phase 3 trial, two were reported during the 120-day safety follow-up period; one resulted in a spontaneous termination where gestational age and fetal condition where unknown, and the other was ongoing. Among the remaining six pregnancies, one ended in a spontaneous abortion where gestational age was unknown, two were electively terminated with no medical reasons provided, and three resulted in full-term, healthy infants.[a]

Patient information for Vumerity™ (diroximel fumarate) states that patients should consult their doctors before or while taking diroximel fumarate if they:[2]

- are pregnant or plan to become pregnant. It is not known if VUMERITY will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if VUMERITY passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using VUMERITY.

Labeling information for Vumerity™ (diroximel fumarate) under "USE IN SPECIFIC POPULATIONS" states:[2]

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

There are no adequate data on the developmental risk associated with the use of diroximel fumarate in pregnant women.[1] In animal studies of rats and rabbits, effects on embryofetal and offspring development, and fetal mortality occurred in conjunction with maternal toxicity and at exposure doses that were at similar, to two-times more than those recommended for humans.[1] Considering that MS is three-times more common in women than in men and more frequently diagnosed in women of childbearing age than any other group,[5,6] data regarding diroximel fumarate in pregnant women with RMS and their offspring is needed.

[a] Information regarding pregnancies during Phase 1 studies and Phase 3 trials were obtained using case narrative for each of the eight subjects.

To date, only a handful of U.S. studies have been published regarding pregnancy outcomes in women with MS.[6-9] Recently, Houtchens, et al. reported a higher proportion of women with MS (N=2,176) had claims for premature labor (31.4% vs. 27.4%; P=0.005), congenital hereditary fetal malformations (13.2% vs. 10.3%; P=0.045) and acquired fetal damage (27.8% vs. 23.5%; P =0.002) compared with women without MS (N=39,377).[6] In an earlier study by Kelly and colleagues, mildly elevated odds of intrauterine growth restriction (odds ratio (OR)=1.7, 95% confidence interval (CI)=1.2-2.4), cesarean delivery (OR=1.3, 95% CI=1.1-1.4), and antenatal hospitalization (OR=1.3, 95% CI=1.2-1.5) was reported among MS women compared with the general obstetric population.[7] However, in two separate U.S. cohort studies, women with MS were no more like to have major pregnancy or delivery complications,[8, 9] nor more likely to have adverse fetal outcomes,[9] compared with women without MS. None of these aforementioned studies considered concurrent medication use. Yet, in a global retrospective MS-based registry cohort study of pregnant women, no differences in spontaneous abortions, term or preterm births were noted among MS women on therapy (N=635) when compared with MS women not on therapy (N=886).[10] This study, however, had a large proportion of pregnancy outcomes (15%) that were unknown, increasing the likelihood of underreporting pregnancies that resulted in miscarriages or induced abortions. Further, assessment of risk using matched non-MS controls was not conducted.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete General ARIA Sufficiency Template.*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Alternative study designs for the electronic database study without chart review would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case-control study.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☐ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes. Because broad-based signal detection is not currently available, other parameters were not assessed.

2.5. Please include the proposed PMR language in the approval letter.

The following language for PMRs related to pregnancy outcomes is in the October 29, 2019, approval letter:[11]

3742-3 Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to diroximel fumarate during pregnancy with two unexposed comparator populations: an internal comparator consisting of women with multiple sclerosis who have not been exposed to diroximel fumarate before or during pregnancy, and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small for gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

1. 3742-4 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3742-3 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to diroximel fumarate during pregnancy compared to an unexposed control population.

3. References

1. New Drug Application (NDA) Clinical Review, Division of Neurology Products. NDA 211855 Diroximel fumarate (monomethyl fumarate). Accessed October 23, 2019.

2. New Drug Application (NDA) Tentative Approval. NDA 211855 Vumerity (diroximel fumarate). Accessed October 23, 2019.

3. Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed October 23, 2019.

4. Alroughani R, Altintas A, Al Jumah M, et al. Pregnancy and the Use of Disease-Modifying Therapies in Patients with Multiple Sclerosis: Benefits versus Risks. Multiple sclerosis international. 2016;2016:1034912.

5. National Multiple Sclerosis Society. Pregnancy and reproductive issues. Available at: nationalmssociety.org/Living-Well-With-MS/Diet-Exercise-Healthy-Behaviors/Womens-Health/Pregnancy. Accessed October 23, 2019.

6. Houtchens MK, Edwards NC, Schneider G, Stern K, Phillis AL. Pregnancy rates and outcomes in women with and without MS in the United States. Neurology 2018;91(17):e1559-e1569.

7. Kelly VM, Nelson LM, Chakravarty EF. Obstetric outcomes in women with multiple sclerosis and epilepsy. Neurology 2009;73:1831–1836.

8. Mueller B, Zhang J, Critchlow C. Birth outcomes and need for hospitalization after delivery among women with multiple sclerosis. Am J Obstet Gynecol 2002;186:446–452.

9. Fong A, Chau CT, Quant C, Duffy J, Pan D, Ogunyemi DA. Multiple sclerosis in pregnancy: prevalence, sociodemographic features, and obstetrical outcomes. J Matern Fetal Neonatal Med 2018;31:382–387.

10. Nguyen A, Havrdova EK, Horakova D, et al. Incidence of pregnancy and disease-modifying therapy exposure trends in women with multiple sclerosis: A contemporary cohort study. Mult Scler Relat Disord 2019;28:235-243.

11. New Drug Application (NDA) Approval. NDA 211855 Vumerity (diroximel fumarate). Accessed October 29, 2019.

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/s/

SARA KARAMI
10/31/2019 12:20:38 PM

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SUKHMINDER K SANDHU
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JUDITH W ZANDER
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10/31/2019 12:30:20 PM

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 8, 2019

To: Sandy Folkendt, Regulatory Project Manager
Division of Neurology Products (DNP)

Tracy Peters, Associate Director for Labeling, (DNP)

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for VUMERITY™ (diroximel fumarate) delayed-release capsules, for oral use (Vumerity)

NDA: 211855/O-1

In response to DNP's consult request dated January 2, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Vumerity.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Sandy Folkendt) on September 24, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate on October 8, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 18, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Christine Bradshaw at (301) 796-6796 or Christine.Bradshaw@fda.hhs.gov.

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/s/

CHRISTINE J BRADSHAW
10/08/2019 01:34:54 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 8, 2019
To:	Billy Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Christine Bradshaw, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VUMERITY (diroximel fumarate)
Dosage Form and Route:	delayed-release capsules, for oral use
Application Type/Number:	NDA 211855
Applicant:	Alkermes, Inc.

1 INTRODUCTION

On December 13, 2018, Alkermes, Inc. submitted for the Agency's review an Original 505(b)(2) New Drug Application (NDA) for VUMERITY (diroximel fumarate) delayed-release capsules, for oral use. The Reference Listed Drug (RLD) is NDA 204063, TECFIDERA (dimethyl fumarate) delayed-release capsules, for use, held by BIOGEN IDEC INC. The Applicant is seeking FDA approval for prescription marketing of the drug product for the treatment of patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on January 2, 2019, for DMPP and OPDP respectively, to review the Applicant's proposed Patient Package Insert (PPI) for VUMERITY (diroximel fumarate) delayed-release capsules, for oral use.

2 MATERIAL REVIEWED

- Draft VUMERITY (diroximel fumarate) PPI received on December 13, 2018 and received by DMPP and OPDP on September 24, 2019.
- Draft VUMERITY (diroximel fumarate) Prescribing Information (PI) received on December 13, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 24, 2019.
- Approved TECFIDERA (dimethyl fumarate) comparator labeling dated July 10, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
10/08/2019 09:25:09 AM

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SHARON W WILLIAMS
10/08/2019 10:25:19 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 2, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211855
Product Name and Strength:	Vumerity (diroximel fumarate) delayed-release capsules, 231 mg
Applicant/Sponsor Name:	Alkermes, Inc.
FDA Received Date:	September 18, 2019
OSE RCM #:	2018-2762-2
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader (Acting):	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling and container labels on September 18, 2019 for Vumerity. The Division of Neurology Products (DNP) requested that we review the revised carton labeling and container labels for Vumerity (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations, and we have no additional recommendations at this time.

[a] Morris, C. Label and Labeling Review for Vumerity (NDA 211855). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 05. RCM No.: 2018-2762-1.

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/s/

JOHN C MORRIS
10/02/2019 11:57:58 AM

BRIANA B RIDER
10/02/2019 10:40:21 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 5, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211855
Product Name and Strength:	Vumerity (diroximel fumarate) delayed-release capsules, 231 mg
Applicant/Sponsor Name:	Alkermes, Inc.
FDA Received Date:	August 16, 2019
OSE RCM #:	2018-2762-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling and container labels on August 16, 2019 for Vumerity. The Division of Neurology Products (DNP) requested that we review the revised carton labeling and container labels for Vumerity (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling and container labels are unacceptable from a medication error perspective. Language can be added or revised to improve clarity, and the size of the barcode containing the NDC number on the container labels can be increased to improve scanability. We provide recommendations for Alkermes, Inc. in Section 3.

[a] Morris, C. Label and Labeling Review for Vumerity (NDA 211855). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 26. RCM No.: 2018-2762.

3 RECOMMENDATIONS FOR ALKERMES, INC.

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for Alkermes, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Commercial Carton Labeling and Container Label			
1.	The proposed mitigations do not adequately differentiate the Starter Pack from the Maintenance Pack.	May increase the risk for wrong quantity, wrong dose, or dose omission medication errors.	We recommend you revise the principal display panel (PDP) to differentiate the commercial starter pack from the maintenance pack. Consider adding the descriptors 'starter dose bottle' and 'maintenance dose bottle' to the PDP of the commercial starter pack and maintenance pack carton labeling, respectively. Alternatively, address this concern by other means.
Container labels			
2.	We acknowledge you increased the amount of white space surrounding the barcode containing the NDC number by decreasing the size of the barcode. However, now the linear barcode containing the NDC number may be too small for scanners to read it.	May increase the risk of wrong drug or wrong quantity medication errors.	Ensure the linear barcode that contains the NDC number can be correctly read by scanners. Consider switching the location of the two barcodes to allow for the size of the linear barcode that contains the NDC number to be increased, or address this concern by other means.
General Carton Labeling and Container Labels (Commercial & Professional Sample)			
3.	The usual dosage statement can be improved.	To ensure consistency with the Physician Labeling Rule (PLR) formatted prescribing information labeling.	Revise the usual dosage statement for the carton labeling and container labels to read: 'Recommended dosage: See prescribing information for dosage and administration'.

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09/05/2019 02:59:19 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 26, 2019

TO: Billy Dunn, M.D.
Director
Division of Neurology Products
Office of New Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of (b) (4) (b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of Studies ALK8700-A103, ALK8700-A104, and ALK8700-A109 (NDA 211855, Diroximel fumarate [ALKS 8700]) conducted at (b) (4)

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

Study ALK8700-A103

"A Phase 1 Study to Determine the Relative Bioavailability of Monomethyl Fumarate Following Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects"
Sample Analysis Period: 08/21/2015 - 09/23/2015

Study ALK8700-A104
"A Phase 1 Study to Assess the Comparative Bioavailability of Monomethyl Fumarate Following Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects Under Fed Conditions"
Sample Analysis Period: 12/8/2015 - 01/11/2016

Study ALK8700-A109
"A Phase 1 Study to Assess the Comparative Bioavailability, Safety and Tolerability of Monomethyl Fumarate Following Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects When Taken with Meals of Varying Fat and Caloric Content"
Sample Analysis Period: 09/22/2016 - 10/27/2016

3. Scope of Inspection

OSIS scientist Melkamu Getie-Kebtie, Ph.D., R.Ph. and ORA Investigator Michael Serrano audited the analytical portion of the above studies at (b) (4) from (b) (4)

The inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff.

4. Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue Form FDA 483 to (b) (4) However, we discussed the following items with management during the inspection and at the close-out meeting.

4.1. Discussion items

We discussed the following items with the firm's management.

4.1.1. The firm did not (b) (4) in the method validation and bioanalytical study reports. Several rejected runs were not reported. Rejected runs identified during inspection are provided in Table 1.

Table 1: List of rejected runs that were not reported in run summary tables

Study	Run ID	Reasons for rejection
Method validation (b) (4) 15040	1	Rejected twice due to IS response sequentially increasing followed by high LC pump pressure
	4	Reinjected in MS instrument ID TQS-3 due to signal saturation of analyte on TQS-1
	13	No peak was observed in some samples and needle placement error was suspected
	14	Significant shift in retention time
Method Validation (b) (4) 15027	9	Suspected impact from matrix
	16	No analyte and IS peak were detected for all samples
	17	High IS response for QCH-4
	19	Rejected twice due to high IS response for QCH-6 followed by instrument communication error
	20	Instrument problem (stopped after only 5 injections)
	23	Rejected twice due to long term stability QC sample was not assigned as QC in Watson sample list followed by curve splitting [a]
	24	Instrument stopped after 1st injection because maximum LC pressure setting was set too low
Sample analysis (b) (4) 15087 (Study ALK8700-A103)	3	Rejected twice due to instrument communication error followed by curve splitting [a]
	4	Instrument communication error
Sample analysis (b) (4) 15151 (Study ALK8700-A104)	1	Abnormal chromatograms (peak shapes)
	2	Abnormal chromatograms (peak shapes)
	8	The injection volume was inadvertently entered as '0' – no peak signal was detected
	13	Curve splitting [a]
Sample analysis (b) (4) 16149 (Study ALK8700-A109)	8	Curve splitting [a]
	13	Instrument communication error
	18	Column deteriorated
	26	Experimental error
	27	Experimental error
	34	Instrument communication error
	41	Instrument communication error
	48	Incorrect plate injected
	72	Run stopped
	73	Peak shape distorted
	87	Run stopped

[a] Curve splitting means all area ratios from each of the two sets of calibration standards laid on opposite side of the regression line of the calibration curve.

Firm's Response: The firm stated that, for reinjected runs, their practice was to report only the final reinjections. Per our advice (b) (4) and reason for failure in the run summary table of bioanalytical study reports, the firm revised their SOP on "Study Report ion". The revised SOP includes a requirement to report (b) (4) in the run summary table.

OSIS Evaluation: The firm's corrective action is acceptable for future studies. During inspection we confirmed that the failed runs and reasons for failure were documented in source records. Therefore, this finding has no impact on reliability of data for the audited studies.

4.1.2. The firm did not use SOP established objective criteria to determine if a run should be rejected and reinjected. The firm used reasons of "Sequentially increasing IS response" and "Curve Splitting" to reject data and reinject samples. However, the firm's SOP for "Repeat Analysis and Reinjection of Samples" (SOP BA 102.01) (b) (4) (b) (4)

1. Sequentially increasing IS response
   - Method validation (b) (4) 15040, Run ID 1 (assessment of linearity, accuracy & precision, sensitivity for RDC-6567)

2. Curve splitting
   - Method validation (b) (4) 15027, Run ID 23 (assessment of long-term stability for 15 days for RDC-5108)
   - Study sample analysis (b) (4) 15087 (Study ALK8700-A103), Run 3 (for RDC-6567 in samples from subjects (b) (6) (b) (6)
   - Study sample analysis (b) (4) 15151 (Study ALK8700-A104), Run 13 (for RDC-6567 in samples from subjects (b) (6)
   - Study sample analysis (b) (4) 16149 (Study ALK8700-A109), Run 8 (for RDC-5108 in samples from subjects (b) (6)

Firm's Response: The firm explained that based on the IS response and calibration curve profiles the analyst decided to reject the runs prior to processing the data in Watson. They said that they were concerned about the potential of accepting a run with curve splitting or sequentially increasing IS response in cases when the run meets run acceptance criteria. They acknowledged that the decision-making processes was somewhat subjective, and they revised their SOP to include a statement that (b) (4) (b) (4) (Attachment 1).

OSIS Evaluation: The firm's corrective action is acceptable for future studies. Per revised SOP, (b) (4)

The decision of rejecting data from the aforementioned runs without prespecified objective criteria raised concern of potential bias to reject undesired data. However, review of source records and project audit trails during inspection confirmed the firm's claim that the decision to reject the data and reinject samples was made prior to quantification of samples from the original runs. In addition, comparison of peak area ratios (peak area of analyte/peak area of internal standard) for the original and reinjected runs collected during inspection demonstrated no marked differences. Therefore, this finding is unlikely to impact reliability of data for samples analyzed in the runs listed above.

4.3 Specific concerns from OND

In the "OSIS Consult Request for Biopharmaceutical Inspections" (Attachment 2), the review division stated their concern that the internal standards used for ALKS 8700 (RDC-5108) and RDC-8439 have different structures and molecular weights and sought justification for their use e asked the firm to justify the use of (b) (4) as internal standards (IS) for RDC-5108 and RDC-8439, respectively. The firm could not provide the rationale for the choice of the IS as the method was developed by (b) (4) and transferred to them. However, they stated that the IS tracked their respective analytes as demonstrated by the acceptable analytical performance from the global accuracy and precision data for RDC-5108 and RDC-8439 in Study ALK8700-A109, causing no concern regarding their appropriateness in quantitation of the analytes.

OSIS Evaluation: The firm's response did not address the question whether the selected ISs track the respective analytes. However, during the inspection, I did not find any indication that the choice of the IS for RDC-5108 and RDC-8439 adversely affected data reliability for Study ALK8700-A109.

5. Conclusion

After review of the inspectional findings, I conclude that data from the audited studies are reliable.

Studies using similar methods conducted between the previous inspection (October 2015) and the end of the current

surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI - (b) (4)

cc: OTS/OSIS/Kassim/Choe/Kadavil/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Getie-Kebtie
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov

Draft: MG 6/28/2019, 7/15/2019, 7/16/2019, 7/22/2019, 7/25/2019
Edit: SA 07/02/2019, 7/15/2019, 7/16/2019, 7/22/2019, 7/25/2019; JC 7/16/2019, 7/23/19, 7/26/19

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/ (b) (4) (b) (4)
OSIS File #: BE 8380

FACTS: 11911076

Attachment
Attachment 1: Modifications to SOP BA 102.07 – (b) (4) (b) (4)

Attachment 2: OSIS Consult Request for Biopharmaceutical Inspections

Attachment 1

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Attachment 2

OSIS Consult Request for Biopharmaceutical Inspections			
Date	4/16/2019		
Subject	Request for Biopharmaceutical Inspections (BE)		
Addressed to	Project Management Staff Office of Study Integrity and Surveillance CDER-OSIS-BEQ@fda.hhs.gov		
Consulting Office/Division	DNP - Division of Neurology Products		
Project Manager	Sandra Folkendt		
PEPFAR?	☐		
Application Type / Num / Sup Num	NDA	211855	Enter Sup Num
Priority Application?	☐		
Drug Product	Diroximel fumarate		
Sponsor Name	Alkermes, Inc.		
Sponsor Address	852 Winter Street, Waltham, MA 02451		
US Agent (if applicable)	Valmik Doshi		
US Agent Address	Click here to enter text.		
Electronic Submission	☒		
GDUFA/PDUFA/BsUFA Goal	10/13/2019		
Action Goal Date	7/12/2019		
Requested Review Goal Date	8/13/2019		

Inspection Request Detail (Complete all applicable fields)	
Study #1	
Study Number	ALK8700-A103
Study Title	A Phase 1 Study to Determine the Relative Bioavailability of Monomethyl Fumarate Following Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects
Study Type	In Vivo BE
Other:	Click here to enter text.
Site #1 Type	Clinical
Site #1 Name	PPD, LP 7551 Metro Center Drive Suite 200 Austin, TX 78744
Select one:	Routine Inspection
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.

Site #2 Type	Analytical
Site #2 Name	(b) (4)
Select one:	Routine Inspection
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #3 Type	Analytical
Site #3 Name	(b) (4)
Select one:	Routine Inspection
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Study Report: (location, eg., 5.3.1.2)	Click here to add report link.
Validation Report: (eg., 5.3.1.2)	Click here to add report link.
Bioanalytical Report: (eg., 5.3.1.4)	Click here to add report link.
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	

Inspection Request Detail (Complete all applicable fields)	
Study #2	
Study Number	ALK8700-A104
Study Title	A Phase 1 Study To Assess The Comparative Bioavailability of Monomethyl Fumarate Following Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects Under Fed Conditions
Study Type	In Vivo BE
Other:	Click here to enter text.
Site #1 Type	Clinical
Site #1 Name	PPD, Inc. 7551 Metro Center Drive Suite 300 Austin, TX 78744
Select one:	Routine Inspection
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.

Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #2 Type	Analytical
Site #2 Name	(b) (4)
Select one:	Routine Inspection
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #3 Type	Analytical
Site #3 Name	(b) (4)
Select one:	Routine Inspection
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Study Report: (location, eg., 5.3.1.2)	Click here to add report link.
Validation Report: (eg., 5.3.1.2)	Click here to add report link.
Bioanalytical Report: (eg., 5.3.1.4)	Click here to add report link.
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	

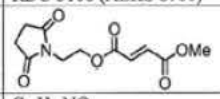
Inspection Request Detail (Complete all applicable fields)	
Study #3	
Study Number	ALK8700-A109
Study Title	A Phase 1 Study to Assess the Comparative Bioavailability,Safety and Tolerability of Monomethyl Fumarate FollowingAdministration of ALKS 8700 and Dimethyl Fumarate inHealthy Subjects When Taken with Meals of Varying Fat and Caloric Content
Study Type	In Vivo BE
Other:	Click here to enter text.

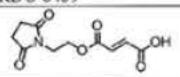
Site #1 Type	Clinical
Site #1 Name	PPD Development, LP
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #2 Type	Analytical
Site #2 Name	(b) (4)
Select one:	
Street	
City	
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #3 Type	Choose an item.
Site #3 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Study Report: (location, eg., 5.3.1.2)	
Validation Report: (eg., 5.3.1.2)	Click here to add report link.
Bioanalytical Report: (eg., 5.3.1.4)	(b) (4) REPORT NUMBER: RPT04128
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	

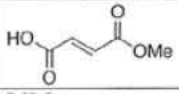
I. Appendix

Specific Items To be Addressed During the Inspection

Bioanalytical Report: (b) (4) REPORT NUMBER: RPT04128
Analytes: RDC-6567, RDC-5108, RDC-8439 and MMF
Using the internal standards (b) (4) (for RDC-5108, ALKS 8700) and (b) (4) (for RDC-8439) needs to be justified. The internal standards seem to have quite different structures and MW (compared to the respective analytes) and might behave differently during the analysis.

Chemical Name	RDC-5108 (ALKS 8700)
Chemical Structure	
Formula	$C_{11}H_{13}NO_6$
Molecular weight (MW)	255.22
Monoisotopic MW	255.07

Chemical Name	RDC-8439
Chemical Structure	
Formula	$C_{10}H_{11}NO_6$
Molecular weight (MW)	241.20
Monoisotopic MW	241.06

Chemical Name	MMF (monomethyl fumarate or fumaric acid monomethyl ester)
Chemical Structure	
Formula	$C_5H_6O_4$
Molecular weight (MW)	130.10
Monoisotopic MW	130.03

2.1.2 Internal Standard

(b) (4)

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/

MELKAMU GETIE KEBTIE
07/26/2019 01:38:55 PM

STANLEY AU
07/26/2019 01:43:56 PM
Team Lead

SEONGEUN CHO
07/26/2019 02:05:15 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 26, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211855
Product Name and Strength:	Vumerity (diroximel fumarate) delayed-release capsules, 231 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Alkermes, Inc.
FDA Received Date:	December 13, 2018
OSE RCM #:	2018-2762
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 REASON FOR REVIEW

As part of the approval process for Vumerity (diroximel fumarate) delayed-release capsules, the Division of Neurology Products (DNP) requested that we review the proposed Vumerity prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

NDA 211855 is a 505(b)(2) NDA and the listed drug product is Tecfidera, NDA 204063.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search ISMP newsletters or FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	(b) (4)		

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Table 3. Identified Issues and Recommendations for Alkermes, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	(b) (4)		

5 CONCLUSION

Our evaluation of the proposed Vumerity prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Alkermes, Inc. so the recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Vumerity that Alkermes, Inc. submitted on December 13, 2018, and the RLD, Tecfidera[a].

Table 4. Relevant Product Information for Listed Drug and Vumerity

Product Name	**Tecfidera**	Vumerity
Initial Approval Date	March 27, 2013	N/A
Active Ingredient	Dimethyl fumarate	Diroximel fumarate
Indication	Treatment of patients with relapsing forms of multiple sclerosis	Treatment of relapsing forms of multiple sclerosis
Route of Administration	Oral	Oral
Dosage Form	Delayed-release capsules	Delayed-release capsules
Strength	120 mg, 240 mg	231 mg
Dose and Frequency	120 mg twice daily for 7 days, the 240 mg twice daily.	1 capsule twice daily for 7 days, then 2 capsules twice daily.
How Supplied	30-day Starter Pack: 120 mg capsules, bottle of 14 capsules 240 mg capsules, bottle of 46 120 mg: bottle of 14 capsules 240 mg: bottle of 60 capsules	30-day Starter Pack (106 capsules) 30-day Maintenance Pack (120 capsules)
Storage	Store at 15°C to 30°C (59 to 86°F). Protect the capsules from light. Store in original container.	Store at (b) (4) (b) (4)
Container Closure[b]	(b) (4)	

[a] Product information for Tecfidera retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204063s020lbl.pdf on June 12, 2019.

[b] Container closure information for Tecfidera retrieved from \\cdsesub1\evsprod\nda204063\0135\m3\32-body-data\32p-drug-prod\dimethyl-fumarate-120mg\32p7-cont-closure-sys\container-closure-system.pdf on June 12, 2019.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 12, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, diroximel fumarate. Our search did not identify any previous reviews.

Additionally, on June 26, 2019 we searched for reviews of the RLD, Tecfidera (dimethyl fumarate), that may be applicable to this review. Our search identified 2 postmarket reviews[c,d] and 6 label and labeling reviews[e,f,g,h,i,j] for Tecfidera. We considered our previous recommendations to see if they are applicable for this current review.

Post-market Reviews

2013-2687 - We identified 26 medication error cases describing overdoses or improper titration due to confusion with the labels and labeling for the Tecfidera 30-day Starter Pack. Recommendations and comments were made to improve clarity surrounding dosing instructions. We confirmed the Sponsor implemented our recommendations.

2015-1535 – We performed a review of wrong frequency errors and underdose errors identified during 915 Safety Review. We made recommendations to the Division of Neurology Products for Section 2.1 (Dosing Information) of the prescribing information improve clarity surrounding dosing instructions for the prescriber and mitigate the risk of wrong dose errors. We confirmed these recommendations were implemented in the Prescribing Information.

Labels and Labeling Reviews

2012-530 - We reviewed the labels and labeling. We provided recommendations to the Sponsor in order to make the dosing instructions on the principal display panels of the container labels more prominent. We reviewed the revised labeling on 11/26/12 (next).

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[c] Sheppard, J. Post-market Medication Error Review for Tecfidera (dimethyl fumarate) NDA 204063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 SEP 05. RCM No.: 2013-2687.

[d] White, L. Post-market Medication Error Review for Tecfidera (dimethyl fumarate) NDA 204063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 11. RCM No.: 2015-1535.

[e] Neshiewat, J. Labels and Labeling Review for Tecfidera (dimethyl fumarate) NDA 204063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 SEP 17. RCM No.: 2012-530.

[f] Neshiewat, J. Labels and Labeling Review for Tecfidera (dimethyl fumarate) NDA 204063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 NOV 26. RCM No.: 2012-530.

[g] Neshiewat, J. Labels and Labeling Review for Tecfidera (dimethyl fumarate) NDA 204063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JAN 15. RCM No.: 2012-530.

[h] Neshiewat, J. Labels and Labeling Review for Tecfidera (dimethyl fumarate) NDA 204063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 FEB 01. RCM No.: 2012-530.

[i] Neshiewat, J. Labels and Labeling Review for Tecfidera (dimethyl fumarate) NDA 204063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 FEB 28. RCM No.: 2012-530.

[j] Morris, C. Labels and Labeling Review for Tecfidera (dimethyl fumarate) NDA 204063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 06. RCM No.: 2016-1707.

2012-530 – We reviewed the revised container labels and carton labeling and determined the Applicant did not implemented all our previous recommendations. We reviewed the revised labeling on 1/15/13 (next).

2012-530 – We review of the revised container labels and carton labeling determined that the Applicant implemented all of our previous recommendations. However, due to the revised placement of information, we identified additional changes that should be made to the container labels and carton labeling to clarify information and ensure that important information is prominent on the labels and labeling. We reviewed the revised labeling on 2/1/13 (next).

2012-530 - We review of the revised container labels and carton labeling. We provided recommendations for the presentation of the established name and dosage form. We reviewed the revised labeling on 2/28/13 (next.

2012-530 - We reviewed the revised container labels and carton labeling. We confirmed the Sponsor implemented our previous recommendations.

2016-1707 - We reviewed the PI. We did not have any recommendations.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Vumerity labels and labeling submitted by Alkermes, Inc. on December 13, 2018.

- Commercial Container labels
- Commercial Carton labeling
- Professional Sample Container label
- Professional Sample Carton labeling
- Prescribing Information (Image not shown)

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JOHN C MORRIS
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BRIANA B RIDER
06/26/2019 02:39:55 PM

Interdisciplinary Review Team for QT Studies Consultation Review

Product	Diroximel fumarate delayed release capsule
Submission Number	NDA 211855/S001
Submission Date	12/13/2018
Date Consult Received	1/10/2019
Clinical Division	Division of Neurology Products (DNP)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review dated 05/10/2018 in DARRTS;
- Investigator's brochure (Submission 0001);
- Proposed label (Submission 0001); and
- Highlights of clinical pharmacology and cardiac safety (Submission 0001).

1 SUMMARY

No significant QTc prolongation effect of diroximel fumarate was detected in this QT assessment. The effect of diroximel fumarate was evaluated in 65 healthy volunteers in Study ALK8700-A110, a placebo- and positive controlled, multiple-dose, parallel group study with a nested crossover design. The highest dose that was evaluated was 924 mg, which is the maximum tolerated dose. The data from ALK8700-A110 was analyzed using exposure-response analysis as the primary analysis, which did not suggest that diroximel fumarate is associated with significant QTc prolonging effect (See Table 1 for overall results). The primary model used the concentration of the major metabolite, RDC-6567, as the exposure metrics. The findings of this analysis are further supported by the available nonclinical data (Section 3.1), central tendency analysis (Section 4.3) and categorical analysis (Section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration	ΔΔ (ms)	90% CI (ms)
QTc	ALKS 8700, 462 mg BID	11.4 ug/mL	-3.7	(-5.9, -1.5)
QTc	ALKS 8700, 924 mg BID	21.4 ug/mL	-4.9	(-7.7, -2.2)
QTc	Moxifloxacin	1959.7 ng/mL	12.93	(9.2, 16.6)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable

2 PROPOSED LABEL

Our changes are highlighted (addition, ~~deletion~~). This is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

(b) (4) Cardiac Electrophysiology

(b) (4)

At a dose 2 times the maximum approved recommended dose, diroximel fumarate does not prolong the QTc interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Diroximel fumarate (also referred to as ALKS 8700 and RDC-5108) is in development for the treatment of relapsing forms of multiple sclerosis. The proposed therapeutic dose is 462 mg twice daily (BID). After oral administration, diroximel fumarate undergoes rapid, pre-systemic hydrolysis to produce two major metabolites, monomethyl fumarate (MMF, active) and 2-hydroxyethyl succinimide (RDC-6567, inactive), and a minor metabolite RDC-8439 (<10% of total diroximel fumarate-related systemic exposure in humans).

The QT-IRT reviewed the QT assessment proposal previously (DARRTS 09/01/2017 and 05/09/2018). The study design and analysis plan were found acceptable.

The sponsor conducted ALK8700-A110, a Phase 1 study, to evaluate the effect of multiple doses of ALKS 8700 on the QTc interval in healthy volunteer. The primary endpoint was QTcF. It is a randomized, double-blind study, which was conducted as a placebo- and positive- (moxifloxacin) controlled, multiple-dose, parallel group study with a nested crossover design. 65 subjects were randomized (2:1:1) to Group 1, Group 2A, and Group 2B, respectively; 52 subjects completed the study.

- Group 1: A single oral dose of moxifloxacin-matching placebo was administered on Days 1 and 12. Oral doses of ALKS 8700 was administered for 10 consecutive days (Days 2 to 11): Days 2 through 6 at the therapeutic dose of 462 mg BID on Days 2 to 5, 462 mg single dose on Day 6, Days 7 through 11 at the supratherapeutic dose of 924 mg BID on Days 7 to 10, and 924 mg single dose on Day 11.
- Group 2A: A single oral dose of 400 mg moxifloxacin was administered on Day 1 and moxifloxacin-matching placebo was administered on Day 12. Oral doses of ALKS 8700-matching placebo were administered for 10 consecutive days (BID on Days 2 to 5 and Days 7 to 10; single dose on Days 6 and 11).
- Group 2B: A single oral dose of moxifloxacin-matching placebo was administered on Day 1 and a single oral dose of 400 mg moxifloxacin was administered on Day 12. Oral doses of ALKS 8700-matching placebo were administered for 10 consecutive days (BID on Days 2 to 5 and Days 7 to 10; single dose on Days 6 and 11).

Electrocardiograms were extracted from the continuous recording by a central ECG laboratory on Days -1 (prior to study medication), 1 (moxifloxacin or placebo), 6 (ALKS 8700 462 mg or placebo), 11 (ALKS 8700 924 mg or placebo), and 12 (moxifloxacin or placebo) at the following time points with matched PK samples (MMF and RDC-6567): predose (-30 minutes) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after dosing.

Based on sponsor's summary of pharmacology, neither diroximel fumarate nor its major inactive metabolites MMF or RDC-6567 inhibited hERG channel activity in vitro (IC_{50} values >300 μM for diroximel fumarate and RDC-6567; IC_{50} >1500 μM for MMF). The estimated safety margins from hERG assays are >160-fold and >5-fold for MMF and RDC-6567, respectively.

Reviewer's comments: Even though the IC50 based safety margins are not very high, the estimates can be limited by the highest concentration tested in the in vitro hERG study. Available data is not adequate to evaluate relative contribution from RDC-6567 or MMF on any potential effects on QTc interval.

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Exposure-response analysis was used for assay sensitivity analysis. The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.5.1 for additional details.

3.2.1.1.1 QT bias assessment

Not applicable.

3.2.2 Categorical Analysis

The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.4 for additional details.

3.2.3 Safety Analysis

No deaths or SAEs occurred during this study. One subject in the ALKS 8700 group experienced an AE of hypersensitivity (deemed moderate and definitely related to study drug by the Investigator) leading to discontinuation.

There was 1 pregnancy (Subject (b) (6)) reported after the End of Study visit (Visit 3; Day 25) by the subject.

***Reviewer's comment**: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

3.2.4 Exposure-Response Analysis

The sponsor evaluated the relationship between ΔQTcF and plasma concentrations of MMF and RDC-6567 using a linear mixed-effects modeling approach. Four models were evaluated. The exposure metrics were MMF alone, RDC-6567 alone, MMF and RDC-6567, MMF plus RDC-6567 and their interactions. The models also include treatment (coded as active = 1 or placebo = 0 regardless of dose levels) and time (each predose and postdose time point on Days 6 and 11) as categorical factors, and random intercept and slopes per subject. The model with MMF and RDC-6567 was selected as the primary model based on AIC. All of the models predicted a lack of small effect at the maximum exposures.

The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e. mean < 10 bpm) were observed (see Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

Not applicable.

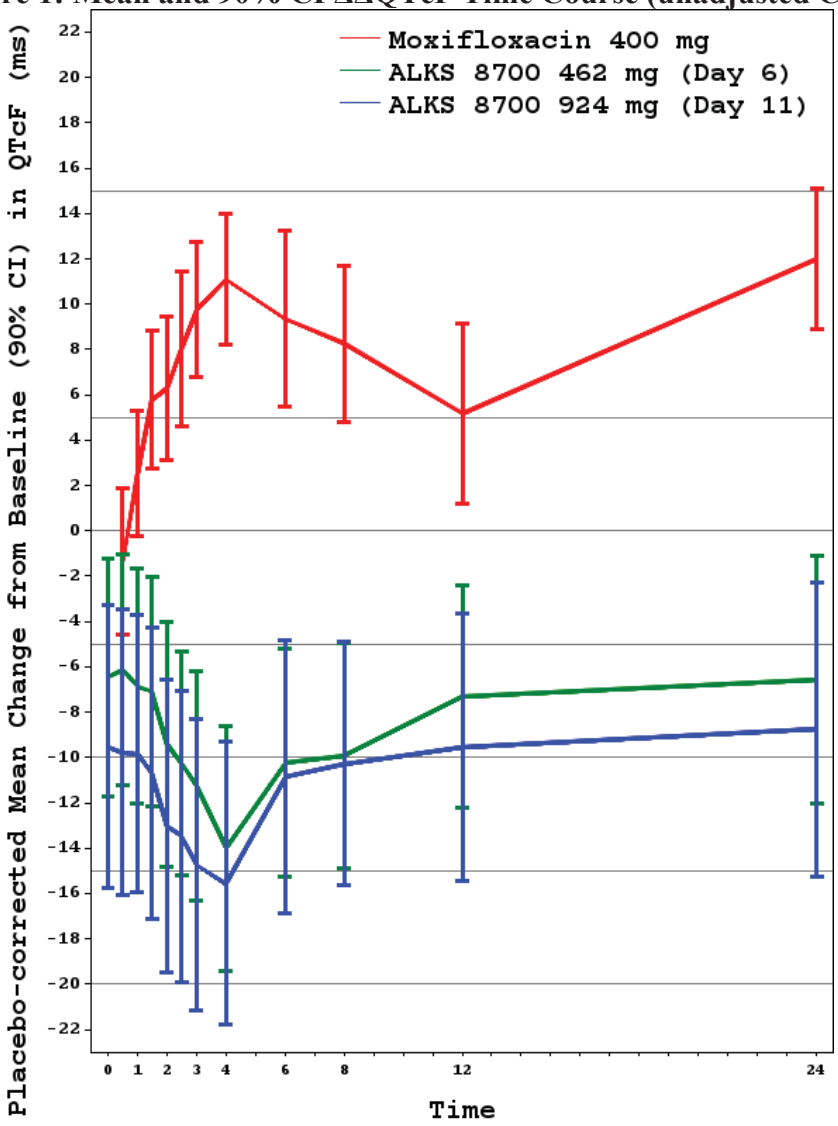
4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The results are a little different from the sponsor's results but both lead to the same conclusions.

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 1: Mean and 90% CI ΔΔQTcF Time Course (unadjusted CIs).



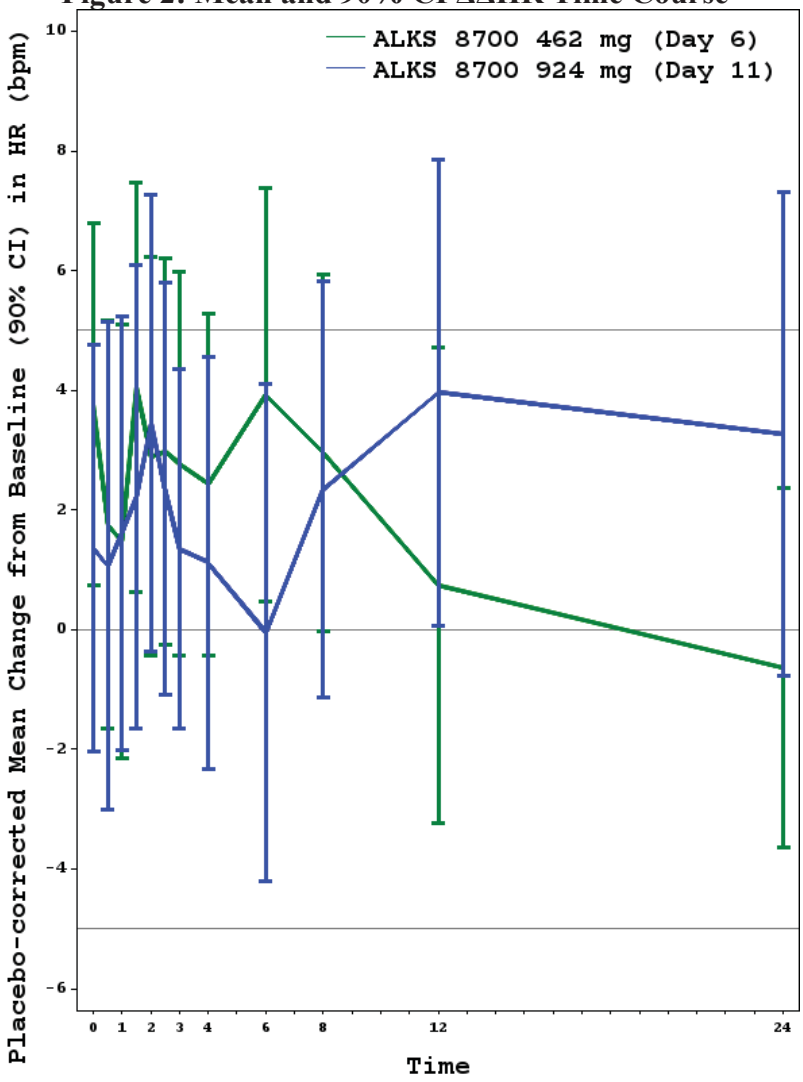
4.3.1.1 Assay sensitivity

The statistical reviewer conducted central tendency analysis for assay sensitivity separately. Mixed model appropriate for crossover design was used in the assessment of assay sensitivity; the model includes sequence, period, treatment, time point, and treatment by timepoint as fixed effects and subject as a random effect. Baseline values are also included as a covariate. The reviewer's results for assay sensitivity was presented in the above Figure 1. The sponsor used exposure response analysis for assay sensitivity assessment. Please see Section 3.2.4 for details.

4.3.2 HR

The same statistical analysis used for the research drug was performed based on HR (Figure 2). The results are similar to that of the sponsor.

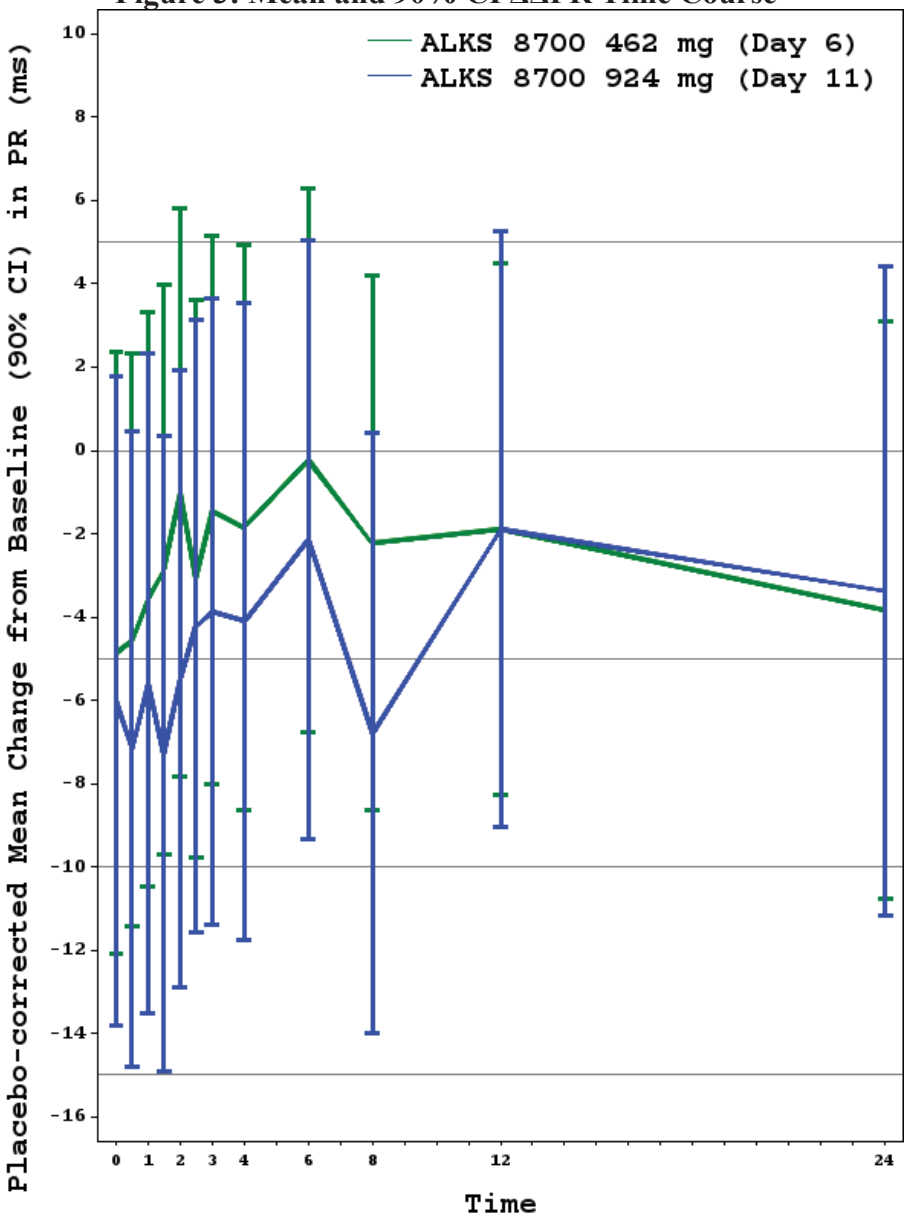
Figure 2: Mean and 90% CI ΔΔHR Time Course



4.3.3 PR

The same statistical analysis used for the research drug was performed based on PR interval (Figure 3). The results are similar to that of the sponsor.

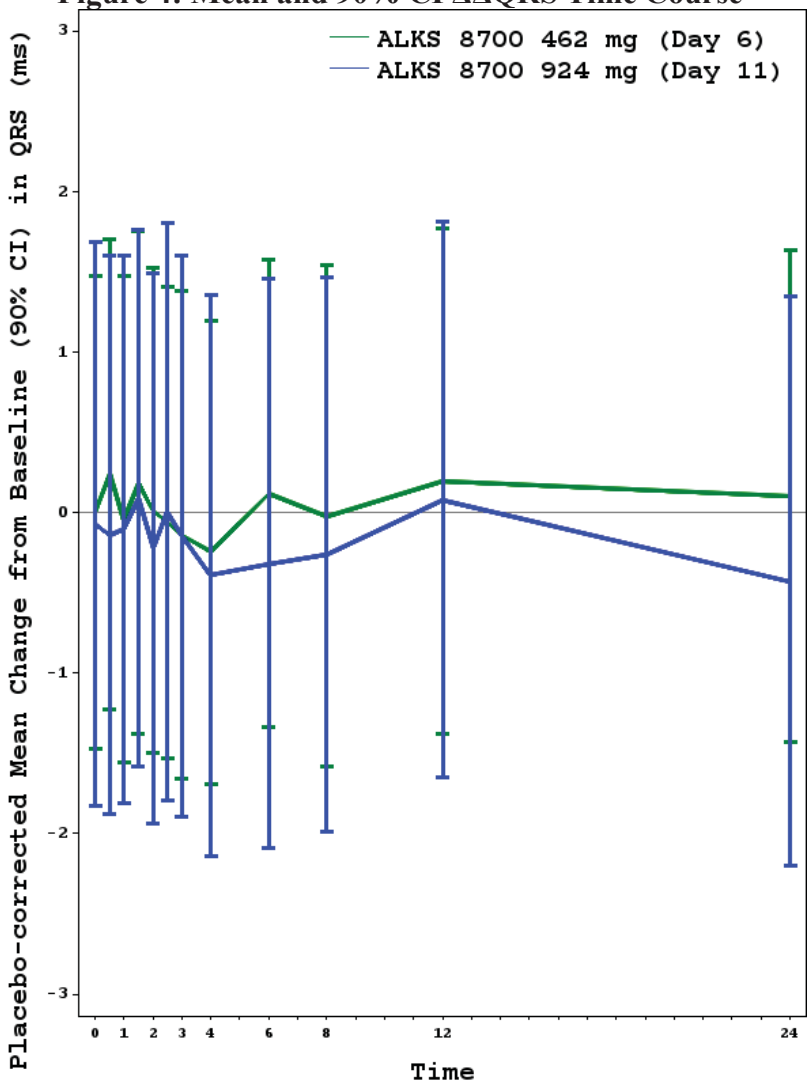
Figure 3: Mean and 90% CI ΔΔPR Time Course



4.3.4 QRS

The same statistical analysis used for the research drug was performed based on QRS interval (Figure 4). The results are similar to that of the sponsor.

Figure 4: Mean and 90% CI ΔΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Except one subject on moxifloxacin placebo in Group 1, no subject's QTcF was above 450 ms in the study. The results are the same as that of the sponsor.

No subject's change from baseline in QTcF (ΔQTcF) was above 30 ms in the study. The results are the same as that of the sponsor.

4.4.2 PR

There were no subjects who experienced PR interval greater than 200 ms in the study. The sponsor listed the total number of subjects as well as the number subjects by timepoint for PR >200 ms with an increase in ΔPR >25%; no outliers were reported for PR based on the sponsor's criteria.

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 2. Four subjects on ALKS 8700 experienced QRS >110 ms on Day 6. Three of the 4 subjects also experienced QRS >110 ms on Day 11 while taking ALKS 8700. The baseline values for these QRS outliers were also >110 ms. The sponsor listed the total number of subjects as well as the number subjects by timepoint for QRS >120 ms with an increase in ΔQRS >25%; no outliers were reported for QRS based on the sponsor's criteria.

Table 2: Categorical Analysis for QRS

Treatment Group	Total N		QRS<=110 ms		QRS>110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline/Predose	65	903	55 (84.6%)	774 (85.7%)	10 (15.4%)	129 (14.3%)
ALKS 8700 462 mg (Day 6)	30	359	26 (86.7%)	315 (87.7%)	4 (13.3%)	44 (12.3%)
ALKS 8700 924 mg (Day 11)	29	348	26 (89.7%)	312 (89.7%)	3 (10.3%)	36 (10.3%)
ALKS 8700 Placebo Pooled	34	777	28 (82.4%)	685 (88.2%)	6 (17.6%)	92 (11.8%)
Moxifloxacin 400 mg	32	351	27 (84.4%)	306 (87.2%)	5 (15.6%)	45 (12.8%)
Moxifloxacin Placebo Pooled	63	1008	52 (82.5%)	879 (87.2%)	11 (17.5%)	129 (12.8%)

4.4.4 HR

The outlier analysis results for HR are presented in Table 3. No subject had HR <=45 bpm in the study. The sponsor listed the total number of subjects as well as the number of subjects by timepoint for HR >100 bpm with an increase in ΔHR >25% and for HR <50 bpm with a decrease in ΔHR >25% on page 88-105 of their cardiac safety report; only one subject on ALKS 8700 placebo had large HR outliers based on the sponsor's criteria.

Table 3: Categorical Analysis for HR

Treatment Group	Total N		HR<=100 bpm		HR>100 bpm	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline/Predose	65	903	64 (98.5%)	901 (99.8%)	1 (1.5%)	2 (0.2%)
ALKS 8700 462 mg (Day 6)	30	359	30 (100%)	359 (100%)	0 (0.0%)	0 (0.0%)
ALKS 8700 924 mg (Day 11)	29	348	28 (96.6%)	347 (99.7%)	1 (3.4%)	1 (0.3%)
ALKS 8700 Placebo Pooled	34	777	33 (97.1%)	771 (99.2%)	1 (2.9%)	6 (0.8%)

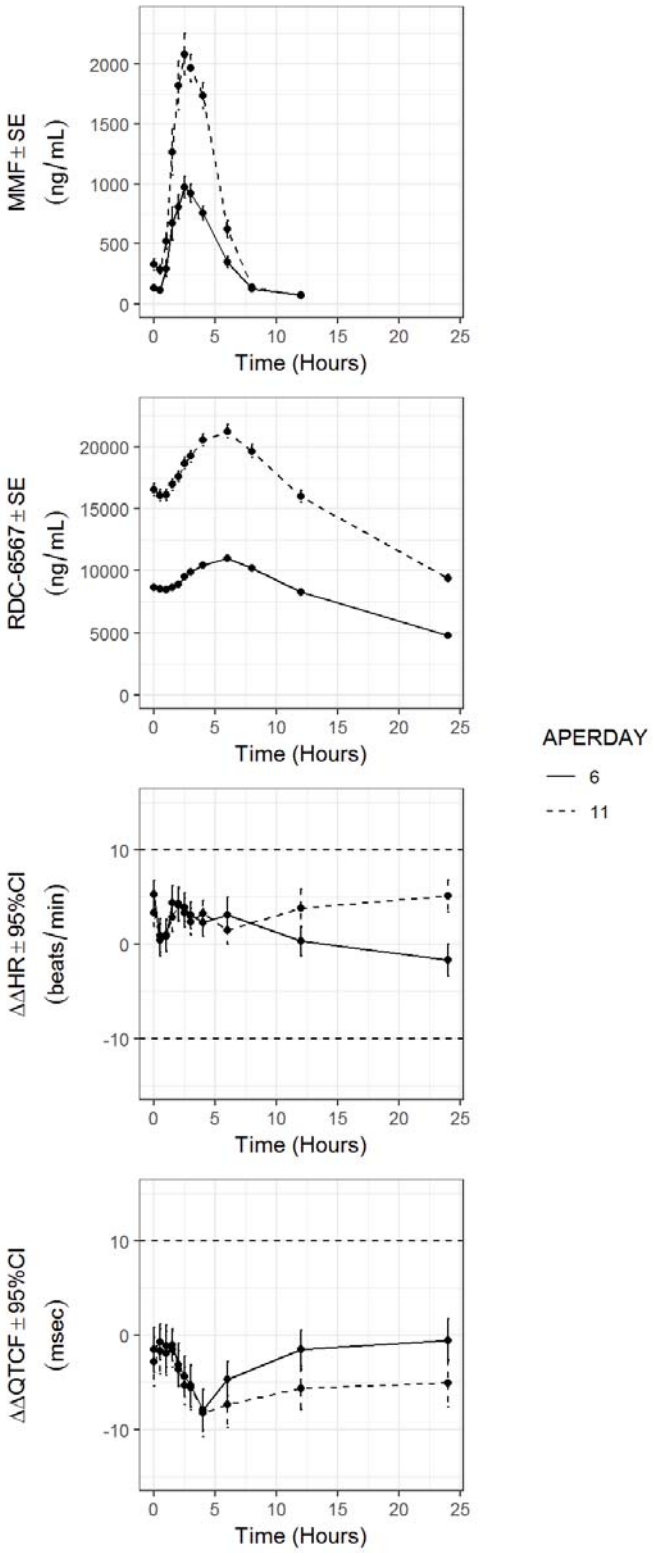
Treatment Group	Total N		HR<=100 bpm		HR>100 bpm	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Moxifloxacin 400 mg	32	351	31 (96.9%)	343 (97.7%)	1 (3.1%)	8 (2.3%)
Moxifloxacin Placebo Pooled	63	1008	62 (98.4%)	1005 (99.7%)	1 (1.6%)	3 (0.3%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between RDC-6567 concentration and ΔQTcF.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship. An evaluation of the time-course of MMF and RDC-6567 concentrations and changes in ΔΔHR and ΔΔQTcF is shown in Figure 5, which shows an absence of significant changes in HR. Additional graphical analysis suggests a lack of significant hysteresis for MMF or RDC-6567 concentrations. The time at maximum effect on ΔΔQTcF appears to correlate better with Tmax of RDC-6567. While there is a clear dose-dependent increase in MMF and RDC-6567 concentrations, the maximum effect on ΔΔQTcF appears similar in the two treatment arms.

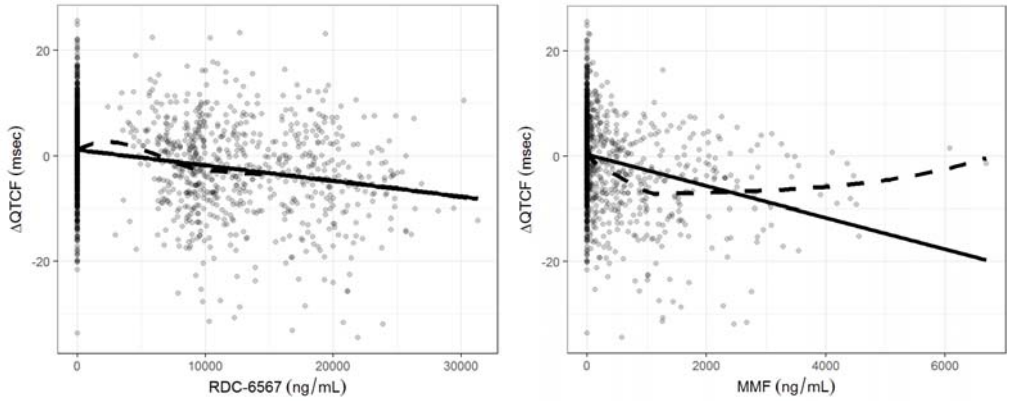
Figure 5: Time course of drug concentration (top two), heart rate (third) and QTcF (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between RDC-6567 concentration and ΔQTcF was evaluated to

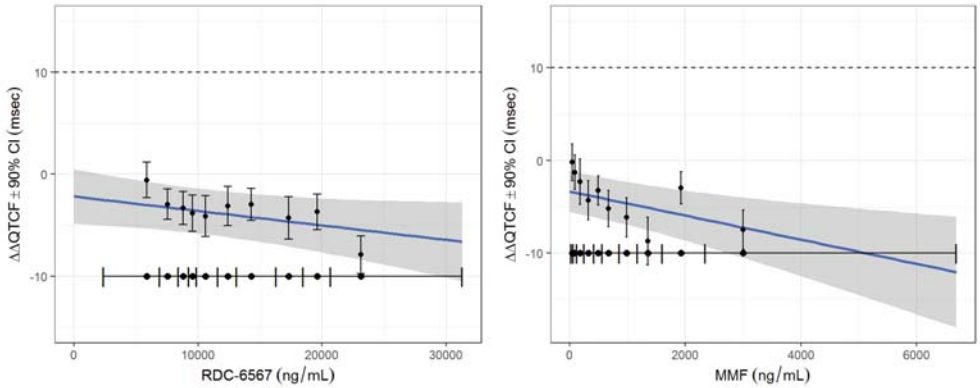
determine if a linear model would be appropriate. Figure 6 shows the relationship between RDC-6567 and MMF concentration and ΔQTcF and supports the use of a linear model. There appears to be less deviation from linearity when ΔQTcF is plotted against RDC-6567 concentration.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. The fixed effects included drug concentration, time since last dose, study day, and baseline adjustment. Random effect from subject ID is placed on the intercept and slope. Predictions from the concentration-QTc model with RDC-6567 concentration are provide in Table 1.

Figure 7: Goodness-of-fit plot for QTc



4.5.1 Assay sensitivity

Assay sensitivity was demonstrated by similar concentration-response analysis of moxifloxacin data at postdose time points on Days 1 and 12. The PK profile and ΔΔQTcF profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (Figure 8). The observed ΔΔQTcF at 24 hours postdose may deviate from the historical profiles, however, its impact on the assessment of linearity appears minimal. The slope of the concentration-QTc model for moxifloxacin was statistically significant at 10% level for 2-sided test and the lower bound of the 2-sided 90% CI of the predicted effect is above 5 ms at the geometrical mean Cmax for moxifloxacin. Study day was not included as a covariate in the linear model.

Figure 8. Time course of moxifloxacin concentration (top), heart rate (middle) and QTcF (bottom)

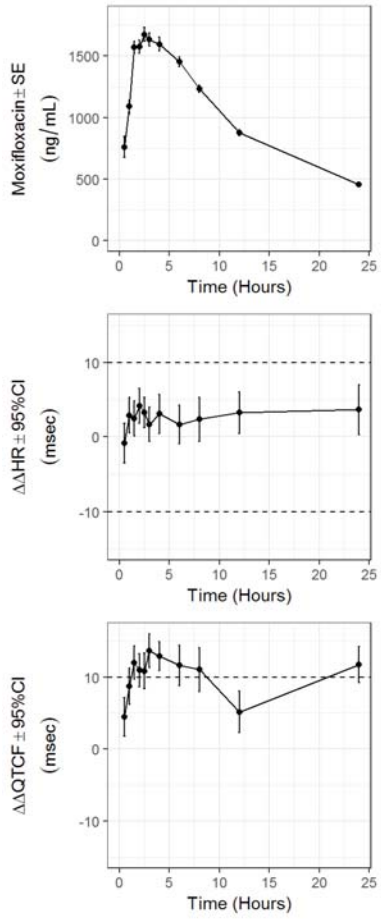
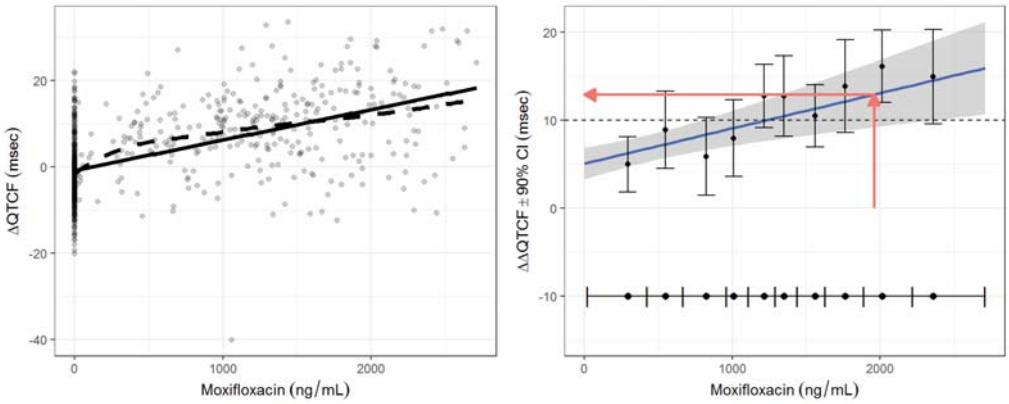


Figure 9: Assessment of linearity of concentration-QTc relationship (Left) and goodness-of-fit plot for QTc (Right) of moxifloxacin



4.6 SAFETY ASSESSMENTS

See section 3.2.3. No additional safety analyses were conducted.

4.7 OTHER ECG INTERVALS

No clinically significant changes in PR or QRS were observed.

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/s/

HONGSHAN LI
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NAN ZHENG
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DALONG HUANG
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MOHAMMAD A RAHMAN
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MICHAEL Y LI
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LARS JOHANNESEN
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CHRISTINE E GARNETT
01/31/2019 02:05:21 PM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 24, 2019

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Dominic Chiapperino, Director
Silvia N. Calderon Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Diroximel fumarate (Vumerity)
NDA 211,855
Indication: Treatment of relapsing-remitting multiple sclerosis
Dosage: 231 mg delayed release oral capsules.
Sponsor: Alkermes Inc. (with Biogen)

Materials reviewed: NDA 211,855 (12/13/18), letter to Sponsor (9/8/17)

I. Background

This memorandum is in response to a consult from the Division of Neurology Products (DNP) regarding the fileability of NDA 211,855 for diroximel fumarate (Vumerity, ALKS 8700, BIIBO98), which is proposed for the treatment of relapsing-remitting multiple sclerosis (RRMS). The dosage form consists of a 231 mg capsule containing (b) (4) (b) (4) each of which contains (b) (4) of diroximel fumarate.

Diroximel fumarate is a prodrug for monomethyl fumarate (MMF), a compound that is the active metabolite of Tecfidera (dimethyl fumarate, DMF), a drug product that is approved for the treatment of RRMS. The Sponsor claims that diroximel fumarate has fewer gastrointestinal adverse events than Tecfidera. The NDA for diroximel fumarate is a 505(b)(2) application that utilizes Tecfidera (NDA 204,063) as the listed drug (LD). The Sponsor states that "Alkermes will rely on the Agency's review of abuse potential for DMF and its metabolite MMF." CSS determined in 2013 that Tecfidera has no abuse potential.

MMF activates the protein called nuclear factor (erythroid-derived 2)-like 2 (Nrf2) that may have antioxidant properties that could reduce damage from oxidative stress. In RRMS, inflammation and oxidative stress contribute to damage to nerve cells and the myelin sheath that insulates

axons. By activating the Nrf2 pathway, MMF may reduce or slow the progressive damage to neurons.

MMF is also the active ingredient in Bafiertam, which received tentative FDA approval on January 2, 2019, after it met the required safety, efficacy, quality, and bioequivalence standards for approval. (Full approval for Bafiertam will be allowed either after Tecfidera patent expiration in June 2020 or after the outcome of pending litigation with Biogen.)

II. Conclusions

There is no need to further evaluate the potential for abuse of diroximel fumarate, based on the following:

- Diroximel fumarate metabolizes to MMF, which is the active moiety responsible for the efficacy of Tecfidera (DMF).

- CSS reviewed the NDA for Tecfidera in 2013 (NDA 204,063) and concluded that DMF (and by extrapolation its active metabolite, MMF) do not have abuse potential.

- Tecfidera was approved on March 27, 2013, with a label that doesn't include Section 9, Drug Abuse and Dependence, reflecting the CSS determination that DMF and MMF do not have abuse potential.

III. Recommendations to the Division

- Given that CSS previously determined that Tecfidera, the RLD for diroximel fumarate, does not have abuse potential, CSS does not need be involved in the review of this NDA. Thus, CSS will not be submitting a filing checklist for diroximel fumarate (NDA 211,855).

- However, CSS requests that the Division consult CSS if the DNP review team identifies any abuse-related concerns associated with the drug through the course of their review of this NDA.

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