CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210296Orig1s000

OTHER REVIEW(S)

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:	April 21, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 210296
Product Name and Strength:	Bafiertam (monomethyl fumarate) delayed-release capsule, 95 mg
Applicant/Sponsor Name:	Banner Life Sciences LLC (Banner)
OSE RCM #:	2018-166-5
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Banner submitted a revised container label received on April 20, 2020 for Bafiertam. The Division of Neurology 2 (DN 2) requested that we review the revised container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to a recommendation we made during a previous label and labeling review.[a]

2 CONCLUSION

Banner implemented our recommendation, and we have no additional recommendations at this time.

[a] Morris, C. Label and Labeling Review MEMO for Bafiertam (NDA 210296). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 10. RCM No.: 2018-166-4.

Reference ID: 4595346

APPENDIX A. IMAGE OF LABEL RECEIVED ON APRIL 20, 2020

Container label

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/

JOHN C MORRIS
04/27/2020 10:37:32 AM

BRIANA B RIDER
04/27/2020 10:47:22 AM

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:	April 23, 2020
Reviewer:	Catherine Callahan, PhD, MA Division of Epidemiology I
Team Leader:	Kira Leishear White, PhD, MS Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Bafiertam (Monomethyl fumarate)
Application Type/Number:	NDA 210296
Sponsor:	Banner Life Sciences
OSE RCM #:	2020-712

Reference ID: 4596874

1. BACKGROUND INFORMATION

1.1. Medical Product

Monomethyl fumarate (Bafiertam, MMF) is the primary active metabolite of dimethyl fumarate (Tecfidera, DMF, NDA 204063, held by Biogen), with the proposed indication to treat relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. While an exact mechanism of action has not been established, MMF appears to exert its therapeutic effects through activation of the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) antioxidant response pathway. Both MMF and DMF are Nrf2 activators.

Tecfidera/DMF was approved to treat relapsing forms of MS on March 27, 2013. The safety profile of MMF, the only known active metabolite of DMF, is thought to be the same as DMF.[1] There is a suggestion that MMF may have a more favorable tolerability profile than DMF, especially with respect to GI tolerability.

As a 505(b)(2) submission, the Sponsor included no studies for MMF to support efficacy and instead the NDA relies entirely on the listed drug, DMF, for evidence of effectiveness. The Sponsor did include six phase one studies to support the safety and pharmacokinetics (PK) of MMF.

The proposed dosage of MMF is 95 mg twice daily orally for seven days. After seven days, the dosage should be increased to the maintenance dosage of 190 mg (administered orally as two 95 mg capsules) twice daily. The proposed labelling for MMF has warnings and precautions for anaphylaxis and angioedema, progressive multifocal leukoencephalopathy, lymphopenia, and liver injury. The proposed labelling for MMF lists the most common adverse reactions reported in two phase two DMF studies as presented in Table 1 below.

Table 1: Adverse Reactions in Study 1 and 2 Reported for Dimethyl Fumarate at ≥ 2% Higher Incidence than Placebo[a]

Adverse Reaction	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

[1] Clinical Review NDA-210296 Bafiertam (monomethyl fumarate)

Aspartate aminotransferase increased	4	2
Lymphopenia	2	<1

[a]Source: Monomethyl fumarate draft labeling as of April 23, 2020. These are DMF studies that are cited in the MMF label.

1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of MMF during pregnancy.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the 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.[2] 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.[3]

There were no animal studies regarding exposure to MMF and pregnancy included in the submission. Dosages of DMF that produced evidence of maternal toxicity (reduced maternal body weight) were associated with embryofetal toxicity (reduced fetal body weight and delayed ossification) in rats and embryolethality in rabbits.

There are no adequate and well-controlled studies that investigated adverse pregnancy outcomes after MMF exposure and a lack of pregnancy studies generally. In all six phase one studies for MMF, a pregnancy test was required prior to the single dose administered, thus no pregnancies were reported.

The current labeling for DMF states "There are no adequate data on the developmental risk associated with the use of TECFIDERA in pregnant women." [4] The Sponsor did not provide any information regarding DMF exposure during pregnancy. There are no postmarketing requirements (PMR) pertaining to pregnancy for DMF. The Biogen Multiple Sclerosis Registry is currently enrolling pregnant women with exposure to DMF or peginterferon beta-1a, which was initiated in response to a pregnancy PMR for peginterferon beta-1a and the Sponsor voluntarily added DMF.[5] FDA is requiring a pregnancy registry for MMF to study patients taking MMF or switch to DMF (or who start on DMF and switch to MMF) to augment the safety database for this therapy.

The Risk Summary in Section 8.1 of the proposed labeling for MMF, as of April 23, 2020 states:

8.1 Pregnancy

Risk Summary

---

[2] 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 11, 2018.

[3] 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.

[4] Tecfidera label as of February 2020 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204063s023lbl.pdf (accessed April 21, 2020)

[5] Biogen Multiple Sclerosis Pregnancy Exposure Registry Protocol 109MS402, June 25 2019

There are no adequate data on the developmental risk associated with the use of BAFIERTAM or dimethyl fumarate (the prodrug of BAFIERTAM) in pregnant women. In animals, adverse effects on offspring survival, growth, sexual maturation, and neurobehavioral function were observed when dimethyl fumarate (DMF) was administered during pregnancy and lactation at clinically relevant doses [see Data].

In the 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. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal data

In rats administered DMF orally (0, 25, 100, and 250 mg/kg/day) throughout organogenesis, embryofetal toxicity (reduced fetal body weight and delayed ossification) were observed at the highest dose tested. This dose also produced evidence of maternal toxicity (reduced body weight). Plasma exposure (AUC) for monomethyl fumarate (MMF), the major circulating metabolite, at the no-effect dose is approximately three times that in humans at the recommended human dose (RHD) of MMF (380 mg/day). In rabbits administered DMF orally (0, 25, 75, and 150 mg/kg/day) throughout organogenesis, embryolethality and decreased maternal body weight were observed at the highest dose tested. The plasma AUC for MMF at the no-effect dose is approximately 5 times that in humans at the RHD of MMF.

Oral administration of DMF (0, 25, 100, and 250 mg/kg/day) to rats throughout organogenesis and lactation resulted in increased lethality, persistent reductions in body weight, delayed sexual maturation (male and female pups), and reduced testicular weight at the highest dose tested. Neurobehavioral impairment was observed at all doses. A no-effect dose for developmental toxicity was not identified. The lowest dose tested was associated with plasma AUC for MMF lower than that in humans at the RHD of MMF.

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 would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case control study

Note: In the PMR language OND/DN2 requested a pregnancy registry with two comparators, an internal comparator group of women with MS and an external comparator group of women without MS, which is why both boxes are checked here.

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 Division of Neurology 2 requests two PMRs related to pregnancy outcomes. As of April 23, 2020, the proposed PMR language for these are:

1. 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 Bafiertam (monomethyl fumarate) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Bafiertam (monomethyl 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.

Draft Protocol Submission:	10/2020
Final Protocol Submission:	06/2021
Annual Interim Report Submissions:	06/2022
	06/2023
	06/2024
	06/2025
	06/2026
	06/2027
	06/2028
	06/2029
	06/2030
	06/2031
Study Completion:	06/2032
Final Report Submission:	06/2033

2. A pregnancy outcomes study using a different study design than provided for in PMR XXXX (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, preterm births, and small-for-gestational-age births in women exposed to Bafiertam (monomethyl fumarate) during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	10/2020
Final Protocol Submission:	06/2021
Annual Interim Report Submissions:	06/2022
	06/2023
	06/2024
	06/2025

	06/2026
	06/2027
	06/2028
	06/2029
	06/2030
	06/2031
Study Completion:	06/2032
Final Report Submission:	06/2033

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/

CATHERINE L CALLAHAN
04/23/2020 11:08:55 AM

KIRA N LEISHEAR
04/23/2020 11:27:54 AM

SUKHMINDER K SANDHU
04/23/2020 11:32:53 AM

JUDITH W ZANDER
04/23/2020 11:46:50 AM

MICHAEL D NGUYEN
04/23/2020 11:57:53 AM

ROBERT BALL
04/23/2020 12:56:31 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:	April 10, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 210296
Product Name and Strength:	Bafiertam (monomethyl fumarate) delayed-release capsule, 95 mg
Applicant/Sponsor Name:	Banner Life Sciences, LLC (Banner)
OSE RCM #:	2018-166-4
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Banner submitted the revised container label, received on April 8, 2020, for Bafiertam. The Division of Neurology 2 (DN 2) requested that we review the revised container label for Bafiertam (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations we made during a previous label and labeling review.[a]

2 FINDINGS AND RECOMMENDATIONS

Table 1, below, contains our medication error concern, the rationale, and proposed recommendation to minimize the risk for medication errors.

[a] Morris, C. Label and Labeling Review for Bafiertam (NDA 210296). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 27. RCM No.: 2018-166-3.

Reference ID: 4590435

Table 1. Identified Issues and Recommendations for Banner Life Sciences (entire table to be conveyed to Banner)		
IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
The principal display panel (PDP) is visually crowded.	Important information on the PDP (that is, "Dispense in original package.", and "Swallow capsules whole.") may be difficult to read and/or easily overlooked due to the lack of adequate white space.	We recommend placing less important information on the secondary display panel of the container label rather than on the PDP. Consider relocating the statements "Recommended Dosage: See prescribing information" and "Each capsule contains 95 mg of monomethyl fumarate" to the secondary display panel.

3 CONCLUSION

Banner implemented all our recommendations; however, we have identified an additional vulnerability. We provide our recommendation in Table 1, above. We ask the Division convey Table 1 to Banner, so the recommendation is implemented prior to approval of this NDA.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 8, 2020

Container label

(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/

JOHN C MORRIS
04/10/2020 03:19:07 PM

BRIANA B RIDER
04/10/2020 03:22:13 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:	March 27, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 210296
Product Name and Strength:	Bafiertam (monomethyl fumarate) delayed-release capsule, 95 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Banner Life Sciences LLC (Banner Life Sciences)
FDA Received Date:	January 9, 2020 and March 2, 2020
OSE RCM #:	2018-166-3
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

Reference ID: 4582411

1 REASON FOR REVIEW

Banner Life Sciences LLC submitted an amendment for Bafiertam (monomethyl fumarate) delayed-release capsule to provide the legal/regulatory basis for a request for final approval. Subsequently, the Division of Neurology 2 (DN 2) requested that we review the proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 210296 is a 505(b)(2) NDA; the listed drug (LD) product is Tecfidera, NDA 204063. NDA 210296 was granted Tentative Approval (TA) on November 16, 2018 because the exclusivity protection of the LD had not expired. Therefore, Banner Life Sciences submitted an amendment to request for final approval, as advised in the TA letter, on January 9, 2020. In their amendment, Banner Life Sciences has updated the agreed upon labeling. These changes are due to revisions in the LD labeling. Additionally, a revised container label was submitted on March 2, 2020, and Banner Life Sciences has decided not to use secondary packaging (i.e., a carton).

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 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 proposed PI and container label, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Reference ID: 4582411

Table 2. Identified Issues and Recommendations for DN 2			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In Section 2.2, the starting dose statement (b) (4)	Can be improved for completeness.	We recommend revising the starting dose statement from: (b) (4) o read "The starting dosage for BAFIERTAM is 95 mg twice a day orally for 7 days."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Some of the storage temperature statements do not contain the unit of measure after each number.	Lack of clarity.	Revise all numeric temperatures to include the respective unit of measure. For example, revise "Store unopened bottles in refrigerator at 2° to 8°C (35° to 46°F)" to read: "Store unopened bottles in refrigerator at 2°C to 8°C (35°F to 46°F)".

Table 3. Identified Issues and Recommendations for Banner Life Sciences LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	The product identifiers required under the Drug Supply Chain Security Act (DSCSA) are not present or denoted by a placeholder.	In September 2018, FDA released draft guidance[a] on product identifiers required under the DSCSA. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and	We recommend that you review the draft guidance[a] to determine if the product identifier requirements apply to your product's labeling. Regarding the expiration date format: To minimize confusion and reduce the risk for

[a] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 3. Identified Issues and Recommendations for Banner Life Sciences LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. [a] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf	deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. The guidance also recommends that the human-readable portion of the product identifier be located near the 2D data matrix barcode and appear in the following format: NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date]
2.	The refrigerate statement can be improved for clarity and is not prominent.	May be overlooked and increase the risk for wrong storage medication errors.	Revise and bold the statement (b) (4) to read "Store unopened container in refrigerator at 2°C to 8°C (36°F to 46°F)."

Table 3. Identified Issues and Recommendations for Banner Life Sciences LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The usual dose statement can be improved.	To ensure consistent language with the Prescribing Information.	Revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."
4.	The strength statement is not prominent.	Not in accordance with 21 CFR 201.15(a)(6).	Increase the prominence of the strength statement taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6).
5.	The established name lacks prominence commensurate with the proprietary name.	Not in accordance with 21 CFR 201.10(g)(2).	Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features the established name to be in accordance with 21 CFR 201.10(g)(2).
6.	The dosage form statement does not appear properly on the container label.	The established name for drug products should include the finished dosage form.[b] [b] The draft guidance is available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf	Place the dosage form statement either on the same line as the active ingredient or directly below it.

5 CONCLUSION

Our evaluation of the proposed Bafiertam PI and container label identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Banner Life Sciences LLC so that recommendations are implemented prior to final approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Bafiertam that Banner Life Sciences LLC submitted on January 9, 2020, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Bafiertam

Product Name	Tecfidera	Bafiertam
Initial Approval Date	March 27, 2013	N/A
Active Ingredient	Dimethyl fumarate	Monomethyl fumarate
Indication	treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
Route of Administration	Oral	Oral
Dosage Form	Delayed-release capsule	Delayed-release capsule
Strength	120 mg, 240 mg	95 mg
Dose and Frequency	120 mg twice daily for 7 days, then 240 mg twice daily	1 capsule (95 mg) twice daily for 7 days, then 2 capsules (190 mg) twice daily
How Supplied	30-day Starter Pack, (NDC 64406-007-03): 7-day bottle 120 mg capsules, quantity 14 23-day bottle 240 mg capsules, quantity 46 120 mg capsules: 7-day bottle of 14 capsules (NDC 64406-005-01) 240 mg capsules: 30-day bottle of 60 capsules (NDC 64406-006-02)	Bottle containing 120 capsules (NDC 69387-001-01)
Storage	Store at 15°C to 30°C (59 to 86°F). Protect the capsules from light. Store in original container.	Store at 2°C to 8°C (35°F to 46°F). Once opened, may be stored at 20°C to 25°C (68°F to 77°F) for up to 3 months.

		Protect capsules from light. Do not freeze
Container Closure	HDPE bottles sealed with an aluminum foil induction seal and white (b) (4) closure	High-density polyethylene (HDPE) bottle that is heat sealed with a tamper evident liner and capped with (b) (4) closure

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 18, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Bafiertam, monomethyl fumarate, and NDA 210296. Our search identified three previous reviews, and we confirmed that our previous recommendations were implemented.

Table 5. Summary of Previous DMEPA Reviews for Bafiertam

OSE RCM #	Review Date	Summary of Recommendations
2018-166[c]	07/27/2018	We reviewed the proposed carton labeling, container label, PI, and PPI, and identified vulnerabilities. We provided recommendations for the PI to DNP and for the carton labeling and container label to Banner Life Sciences.
2018-166-1[d]	10/12/2018	We reviewed revised carton labeling and container label and found deficiencies. We provided recommendations regarding lot/exp statements and a product quality warning to Banner Life Sciences.
2018-166-2[e]	11/16/2018	We reviewed revised carton labeling and container label and found deficiencies. We provided recommendations regarding the "Rx Only" statement to Banner Life Sciences.

[c] Morris, C. Label and Labeling Review for Bafiertam (monomethyl fumarate) NDA 210296. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 27. RCM No.: 2018-166.

[d] Morris, C. Label and Labeling Review for Bafiertam (monomethyl fumarate) NDA 210296. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 12. RCM No.: 2018-166-1.

[e] Morris, C. Label and Labeling Review for Bafiertam (monomethyl fumarate) NDA 210296. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 16. RCM No.: 2018-166-2.

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,[f] along with postmarket medication error data, we reviewed the following Bafiertam labels and labeling submitted by Banner Life Sciences LLC.

- Container label received on March 2, 2020
- Prescribing Information (Image not shown) received on January 9, 2020[g]

F.2 Label and Labeling Images

Container label

(b) (4)

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

[g] Available in EDR via: \\cdsesub1\evsprod\nda210296\0039\m1\us\section-11413-bafiertam-nda-210296-pi-fda-editorial-edi.docx

---

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/

JOHN C MORRIS
03/27/2020 12:13:16 PM

BRIANA B RIDER
03/28/2020 03:25:43 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:	October 10, 2018
To:	Billy Dunn, M.D., Director Division of Neurology Products
Through:	Dominic Chiapperino, Acting Director Martin Rusinowitz, M.D., Senior Medical Officer Controlled Substance Staff
From:	Silvia N. Calderon Ph.D., Senior Pharmacologist Controlled Substance Staff
Subject:	NDA 210296, Bafiertam (monomethyl fumarate) delayed-release capsules **Indication:** Treatment of patients with relapsing forms of multiple sclerosis **Dosages:** 95 mg delayed release oral capsules. **Sponsor:** Banner Life Sciences LLC
Materials reviewed:	NDA 210296 for filing purposes. NDA 204063, Reference listed drug Tecfidera (Dimethyl Fumarate), CSS Reviews (DAARTS, Lerner, Alicja, 10/20/2012; Randall-Thompson, 03/06/2015 and 08/25/2015)

I. Background

This memorandum is in response to a consult request dated January 29, 2018 from the Division of Neurology Products (DNP) pertaining the fileability of NDA 210296, Bafiertam (Monomethyl fumarate delayed-release oral capsules), in lieu of a filing checklist.

Monomethyl fumarate (MMF) is the active metabolite of Tecfidera (dimethyl fumarate[DMF]), the reference listed drug for this 505 (b) (2).

II. Conclusions

1. There is no need to further evaluate the potential for abuse of MMF, based on the following:
   a. MMF is considered the active moiety responsible for the efficacy of DMF.
   b. DMF rapidly metabolizes to MMF, as DMF is not quantifiable in plasma following oral administration.

Reference ID: 4332906

c. CSS previously reviewed the reference listed drug (DMF) under NDA 204063 and concluded that DMF and by extrapolation its active metabolite (MMF) did not have abuse potential.
d. DMF was approved on March 27, 2013 and, concordant with its lack of potential for abuse, the label for Tecfidera doesn't not include a Section 9.0, Drug Abuse and Dependence.

III. Recommendations to the Division

Based on CSS's prior findings for Tecfidera, the reference listed drug for this NDA, and the findings included above, we believe that CSS need not be involved in the review of this NDA. Consequently, CSS will not submit a filing checklist for NDA 210296.

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.

Reference ID: 4332906

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/

SILVIA N CALDERON
10/10/2018

DOMINIC CHIAPPERINO
10/23/2018

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

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

Memorandum

Date: October 16, 2018

To: Sandra 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, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for BAFIERTAM (monomethyl fumarate) delayed-release capsules, for oral use

NDA: 210296/O-1

In response to DNP's consult request dated August 29, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide and carton and container labeling for the original NDA submission for BAFIERTAM (monomethyl fumarate) delayed-release capsules, for oral use (Bafiertam).

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DNP (Sandra Folkendt) on October 3, 2018, and comments on the proposed PI are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on October 16, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 1, 2018, and comments are provided below.

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

24 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

CHRISTINE J BRADSHAW
10/16/2018

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 15, 2018
To:	William 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)**
From:	Sharon W. Williams, MSN, BSN, RN Senior 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):	BACFIERTAM (monomethyl fumarate)
Dosage Form and Route:	delayed-release capsule, for oral use
Application Type/Number:	NDA 210296
Applicant:	Banner Life Sciences LLC

1 INTRODUCTION

On January 18, 2018, Banner Life Sciences LLC submitted for the Agency's review an Original 505(b)(2) New Drug Application (NDA) for BAFIERTAM (monomethyl fumarate) Delayed-Release Capsules. The Applicant is seeking FDA approval for prescription marketing of the drug product for the treatment of patients with relapsing forms of multiple sclerosis.

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 October 3, 2018, for DMPP and OPDP to review the Applicant's proposed PPI for BACFIERTAM **(**monomethyl fumarate**)** Delayed-Release Capsules.

2 MATERIAL REVIEWED

- Draft BACFIERTAM (monomethyl fumarate) PPI received on January 18, 2018, and received by DMPP and OPDP on October 5, 2018.
- Draft BACFIERTAM (monomethyl fumarate) Prescribing Information (PI) received on January 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 5, 2018.
- Approved compartor labeling TECFIDERA (dimethyl fumarate) delayed-release capsules dated December 12, 2017.

3 REVIEW METHODS

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 documents 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 labelings 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.

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

SHARON W WILLIAMS
10/15/2018

CHRISTINE J BRADSHAW
10/16/2018

LASHAWN M GRIFFITHS
10/16/2018

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: October 2, 2018

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

Through: Dominic Chiapperino, Acting Director
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Silvia N. Calderon Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: NDA 210296, Bafiertam (monomethyl fumarate) delayed-release capsules
Indication: For the treatment of patients with relapsing forms of multiple sclerosis
Dosages: 95 mg delayed release oral capsules.
Sponsor: Banner Life Sciences LLC

Materials reviewed: NDA 210296 for filing purposes.
NDA 204063, Reference listed drug Tecfidera (Dimethyl Fumarate), CSS Reviews (DAARTS, Lerner, Alicja, 10/20/2012; Randall-Thompson, 03/06/2015 and 08/25/2015)

I. Background

This memorandum is in response to a consult request dated January 29, 2018, from the Division of Neurology Products pertaining the fileability of NDA 210296, Bafiertam (Monomethyl fumarate delayed-release oral capsules), and in lieu of a filing checklist.

Monomethy fumarate (MMF) is the active metabolite of Tecfidera (dimethyl fumarate, DMF), the reference listed drug for this 505 (b) (2).

II. Conclusions

1. There is no need to further evaluate the potential for abuse of MMF, based on the following:
   a. MMF is considered the active moiety responsible for the efficacy of Tecfidera (DMF).

Reference ID: 4329063

b. DMF rapidly metabolizes to MMF, as DMF is not quantifiable in plasma following oral administration.
c. CSS previously reviewed the reference listed drug (DMF) under NDA 204063 and concluded that DMF and by extrapolation its active metabolite (MMF) did not have abuse potential.
d. DMF was approved on March 27, 2013 and concordant with its lack of potential for abuse, the label for Tecfidera doesn't not include a Section 9.0, Drug Abuse and Dependence.

III. Recommendations to the Division

Based on CSS's prior findings for Tecfidera the reference listed drug for this NDA and findings stated above, we believe that CSS need not be involved in the review of this NDA. Consequently, CSS will not submit a filing checklist for NDA 210296.

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.

Reference ID: 4329063

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/

SILVIA N CALDERON
10/02/2018

MARTIN S RUSINOWITZ
10/02/2018

DOMINIC CHIAPPERINO
10/04/2018

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:	July 27, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210296
Product Name and Strength:	Bafiertam (monomethyl fumarate) delayed-release capsule 95 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Banner Life Sciences, LLC
FDA Received Date:	January 18, 2018 and April 20, 2018
OSE RCM #:	2018-166
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

Reference ID: 4297289

1 REASON FOR REVIEW

This review evaluates the proposed carton labeling and container labels, Prescribing Information (PI), and Patient Information for NDA 210296, Bafiertam (monomethyl fumarate), for areas of vulnerability that may increase the risk for medication errors. This review is written in response to a request from the Division of Neurology Products (DNP).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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 (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed carton labeling and container labels, PI, and Patient Information identified the following areas that can be improved to decrease risk of medication error and to align with Federal Regulations:

Container Label

- The container label does not contain:
  - Strength statement per 21 CFR 201.15(a)(6)
  - Linear barcode per 21 CFR 201.25
  - Usual dose statement per 21 CFR 201.55
  - Manufacturer information per 21 CFR 201.1(a)
  - Placeholder for lot # per 21 CFR 201.10(i)(1)

Carton Labeling

- The usual dose statement, as presented, is misleading and may contribute to wrong dose medication error.

Carton Labeling and Container Label

Reference ID: 4297289

- The expiration date format is presented by placeholders on the container label (xx/xxxx) and carton labeling (MM/YY).

HPI and PI

- The language used in the HPI Dosage and Administration, Section 2.1 Dosing Information, Section 17 Patient Counseling Information, and Patient Information to instruct on the administration of the product (e.g. swallow whole) can be better presented to decrease risk of wrong technique medication error.
- The product descriptions in Section 3 and Section 16 are inconsistent.

We provide recommendations in Sections 4.1 and 4.2 to address these concerns and reduce the risk for medication errors with the use of Bafiertam.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the container label, carton labeling, and PI that can be improved to add required information, improve clarity for administration of the product, reduce the potential for confusion during product identification and increase consistency in the labeling to mitigate the potential for medication errors and promote the safe and effective use. We also identified areas where product information should be added to the labeling to align with Federal regulations. We provide recommendations below to address our concerns. We advise these recommendations are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION OF NEUROLOGY PRODUCTS

A. Prescribing Information
   1. Highlights (HPI) of the prescribing information, Full Prescribing Information (PI)
      a. The HPI Dosage and Administration, Section 2 Dosing Information, Section 17 Patient Counseling Information and within the Patient Information How Should I take BAFIERTAM subsection can be improved to better instruct on the proper administration of the product. As presented, the administration instructions read:

(b) (4)

         We recommend the language is revised throughout the labeling to read:

         BAFIERTAM should be swallowed whole. Do not crush, chew, or mix contents with food."

      b. Section 3 and Section 16 contains inconsistent product identifier information. The description of the product identifying information per each capsule in Section 3 states: "The 95 mg capsule is a white, opaque, oval, coated (b) (4), printed with "#" in black ink on the body." However, the description in Section 16 states: BAFIERTAM is available as soft gelatin delayed-release capsules containing 95 mg of

Reference ID: 4297289

monomethyl fumarate. [redacted] We recommend these sections contain the same description of the dosage form to decrease risk of confusion.

4.2 RECOMMENDATIONS FOR BANNER LIFE SCIENCES, LLC

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

A. Container labels & Carton Labeling
   1. As currently presented, the format for the expiration date is defined by placeholders. To reduce the risk for degraded drug medication errors, identify the format you intend to use. We recommend using a format like:
      - DDMMMYYYY (e.g., 31JAN2013),
      - MMMYYYY (e.g., JAN2013),
      - YYYY-MMM-DD (e.g., 2013-JAN-31), or
      - YYYY-MM-DD (e.g., 2013-01-31).

B. Container Labels
   1. We recommend you add the following required information to the container label:
      a. Strength per 21 CFR 201.15(a)(6),
      b. Linear barcode per 21 CFR 201.25,
      c. Usual dose statement per 21 CFR 201.55,
      d. Manufacturer information per 21 CFR 201.1(a),
      e. Placeholder for lot # per 21 CFR 201.10(i)(1).

C. Carton Labeling
   1. As currently presented, the usual dose statement is misleading since the proposed dosing regimen consists of different initiation and maintenance doses. We recommend you remove [redacted] and we also recommend you revise the [redacted] dosage language to read: "[redacted] dosage: See prescribing information."

Reference ID: 4297289

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bafiertam received on April 20, 2018 from Banner Life Sciences, and the listed drug (LD).

Table 2. Relevant Product Information for Bafiertam and the Listed Drug

Product Name	**Bafiertam**	**Tecfidera**
Initial Approval Date	N/A	March 27, 2013
Active Ingredient	Monomethyl fumarate	Dimethyl fumarate
Indication	treatment of patients with relapsing forms of multiple sclerosis	treatment of patients with relapsing forms of multiple sclerosis
Route of Administration	Oral	Oral
Dosage Form	Delayed-release capsule	Delayed-release capsule
Strength	95 mg	120 mg, 240 mg
Dose and Frequency	1 capsule (95 mg) twice daily for 7 days, then 2 capsules (190 mg) twice daily	120 mg twice daily for 7 days, then 240 mg twice daily
How Supplied	30-day bottle of 120 capsules (NDC 69387-001-01)	30-day Starter Pack, (NDC 64406-007-03): 7-day bottle 120 mg capsules, quantity 14 23-day bottle 240 mg capsules, quantity 46 120 mg capsules: 7-day bottle of 14 capsules (NDC 64406-005-01) 240 mg capsules: 30-day bottle of 60 capsules (NDC 64406-006-02)
Storage	Store at (b) (4) Protect the capsules from light. Store in original container.	Store at 15°C to 30°C (59 to 86°F). Protect the capsules from light. Store in original container.
Container Closure	High-density polyethylene (HDPE) bottle that is heat	HDPE bottles sealed with an aluminum foil induction seal

Reference ID: 4297289

	sealed with a tamper evident liner and capped (b) (4)	(b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Bafiertam labels and labeling submitted by Banner Life Sciences.

- Container label received on January 18, 2018
- Carton labeling received on January 18, 2018
- Prescribing Information (Image not shown) received on April 20, 2018

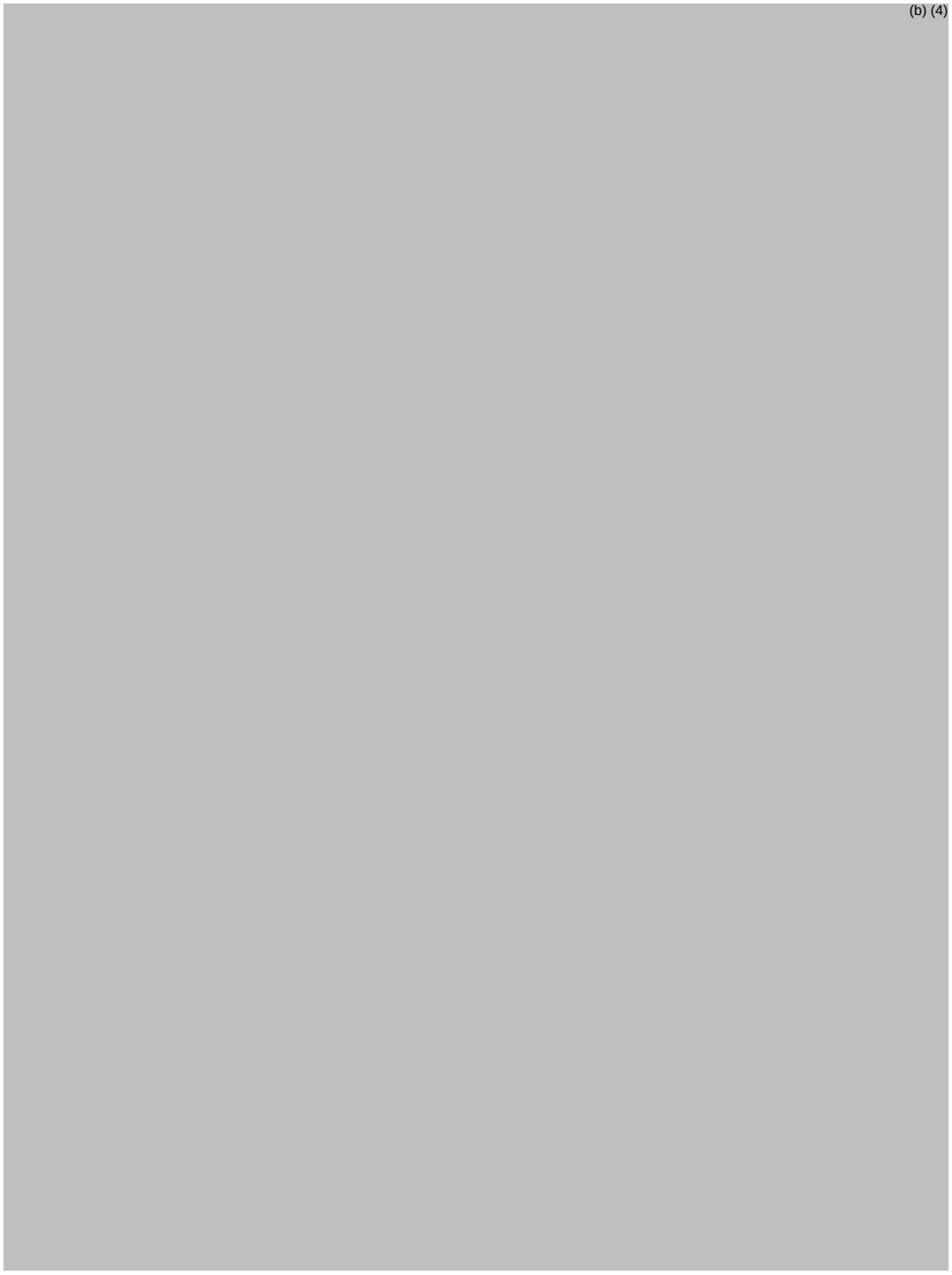
[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 4297289

G.2 Label and Labeling Images

Container label

(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/

JOHN C MORRIS
07/27/2018

LOLITA G WHITE
07/27/2018

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: 4/24/2018

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 210296

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Celerion	2420 West Baseline Road, Tempe, AZ
Analytical	(b) (4)	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
04/24/2018