CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214869Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: October 29, 2021

To: Leonard Kapcala, M.D.
Division of Neurology I (DN I)

Stacy Metz, Regulatory Project Manager, (DRO-N)

Tracy Peters, Associate Director for Labeling, (DN I)

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for DHIVY (carbidopa and levodopa) tablets, for oral use

NDA: 214869

In response to DN I consult request dated December 16, 2020, OPDP has reviewed the proposed product labeling (PI) and container labeling for the original NDA for Dhivy (carbidopa and levodopa) tablets, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN I (Stacy Metz) on October 19, 2021, and are provided below.

Container Labeling: OPDP has reviewed the attached proposed container labeling submitted by the Sponsor to the electronic document room on June 22, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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SAMUEL A FASANMI
10/29/2021 04:10:49 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:	June 29, 2021
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 214869
Product Name and Strength:	Dhivy (carbidopa and levodopa) tablet, 25 mg/100 mg
Applicant/Sponsor Name:	Riverside Pharmaceuticals Corporation
OSE RCM #:	2020-2204-2
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on June 22, 2021 for Dhivy. Division of Neurology 1 (DN 1) requested that we review the revised container label for Dhivy (Appendix A) to determine if it is 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.

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[a] Morris, C. Label and Labeling Review for carbidopa and levodopa (NDA 214869). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 08. RCM No.: 2020-2204-1.

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JOHN C MORRIS
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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:	June 8, 2021
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 214869
Product Name and Strength:	carbidopa and levodopa[a] tablet, 25 mg/100 mg
Applicant/Sponsor Name:	Riverside Pharmaceuticals Corp
OSE RCM #:	2020-2204-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on May 12, 2021 for carbidopa and levodopa. Division of Neurology 1 (DN 1) 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 recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised container label is unacceptable from a medication error perspective. The prominence of the established name, the strength, and usual dose statements can be improved. We provide recommendations for Riverside Pharmaceuticals Corp in Section 3, below.

3 RECOMMENDATIONS FOR RIVERSIDE PHARMACEUTICALS CORP

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

[a] Proprietary name currently under review.
[b] Morris, C. Label and Labeling Review for carbidopa and levodopa (NDA 214869). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 28. RCM No.: 2020-2204.

Table 1. Identified Issues and Recommendations for Biohaven Pharmaceuticals Corp (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label – Principle Display Panel			
1.	The established name lacks prominence commensurate with the proprietary name.	The established name is not presented 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 in accordance with 21 CFR 201.10(g)(2).
2.	The presentation of the letters, "D" and "h" in the proposed proprietary name, Dhivy, can be improved for readability.	The artistic presentation of the letters "D" and "h" may detract from the readability and may distort the interpretation of the proprietary name.	We recommend you reconsider the font or styling used in the presentation of the proprietary name.
3.	The strength does not contain a space between the numbers and unit of measure.	There is not adequate space between the number and unit of measure for readability.	Add a space between the number and unit of measure portions of the strength statement, to read: 25 mg/100 mg
Container label – Side Panel			
3.	The statement, "(b) (4) [redacted] " can be improved.	Labels for prescription drugs are required to bear a statement of the recommended or usual dosage per 21 CFR 201.100(b)(2). Furthermore, to ensure consistency with the Physician Labeling Rule (PLR) formatted prescribing information, we recommend the phrase "Recommended Dosage: See prescribing information."	Revise the statement: [redacted] (b) (4) " to read "Recommended Dosage: See prescribing information".

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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:	April 28, 2021
Requesting Office or Division:	Division of Neurology 1 (DN1)
Application Type and Number:	NDA 214869
Product Name and Strength:	carbidopa and levodopa[a] tablet, 25 mg/100 mg
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Riverside Pharmaceuticals Corp
FDA Received Date:	October 14, 2020
OSE RCM #:	2020-2204
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

[a] Proprietary name currently under review.

1 REASON FOR REVIEW

As part of the approval process for carbidopa and levodopa tablet, the Division of Neurology 1 (DN1) requested that we review the proposed Prescribing Information (PI) and container label for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

NDA 214869 is a 505(b)(2) NDA and the listed drug product is Sinemet, NDA 17555.

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

Table 2. Identified Issues and Recommendations for DN1

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The proposed proprietary name, (b) (4), is contained within the labeling.	The proposed proprietary name, (b) (4), was denied.	Replace "(b) (4)" with the proprietary name that is eventually found acceptable throughout the PI.
Highlights of Prescribing Information			
1.	The Dosage and Administration section does not contain any dosing information.	We are concerned that the lack of dosing information might result in wrong dose medication errors.	We recommend adding the initial recommended dose and dose titration information to this section.

Table 2. Identified Issues and Recommendations for DN1			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2.1 states "(b) (4) [redacted]" and does not contain a corresponding numerical strength for one tablet.	We are concerned that users will not know if one tablet corresponds to a whole tablet or a portion of a tablet broken at the scored location.	We recommend revising the statement to read "The recommended initial dose is one, unbroken, 25 mg/100 mg carbidopa/levodopa tablet three times a day".
2.	Section 2.2 is not informative from a dosing perspective.	Can be improved for clarity.	If the statement of (b) (4) [redacted] is necessary, then we recommend stating the (b) (4) [redacted].
3.	Section 2.3 does not contain a unit of measure after each number.	Can be improved for clarity.	We recommend adding the unit of measure, mg, after the number "(b) (4) [redacted]".
Full Prescribing Information – Section 17 Patient Counseling			
1.	Dosing Instructions do not contain (b) (4) [redacted] information.	Can be improved for clarity.	If the (b) (4) [redacted] statement in 2.2 is necessary, then we recommend adding similar language to the Dosing Instructions section.

Table 3. Identified Issues and Recommendations for Riverside Pharmaceuticals Corp (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label – Principle Display Panel			
1.	The established name lacks prominence commensurate with the proprietary name.	The established name is not at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).	Increase the prominence of the established name taking into account all pertinent factors, including typography (for example, the Rx only and net quantity statements are more prominent), layout (you may consider moving the ingredient and storage statements to the side panel), contrast, and other printing features.

Table 3. Identified Issues and Recommendations for Riverside Pharmaceuticals Corp (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The strength lacks prominence.	As currently presented, we are concerned the strength might be overlooked and it is not in accordance with 21 CFR 201.15(a)(6).	Increase the prominence of the strength.
3.	The strength does not contain the unit of measure, mg.	The strength statement is incomplete.	Add the unit of measure, mg, to the strength statement. Ensure there is adequate space between the number and unit of measure.
4.	The dosage form statement is incorrect.	The proper dosage form is "tablet".	Revise the dosage form statement to "tablet".
Container label – Side Panel			
1.	The panel that includes the linear barcode is cluttered and decreases the prominence of the usual dose statement.	The readability of the usual dose statement can be improved.	We recommend you increase the prominence of the usual dose statement. Consider options like reducing the size of the linear barcode or moving the usual dose statement to the other side panel.
2.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends the format of the human-readable portion be located near the 2D data matrix barcode as follows: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]	We recommend you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf If you determine that the product identifier requirements apply to your product's labeling, add a placeholder for the human- and machine-readable product identifiers to your product's labeling. Pay particular attention to our recommended expiration date format.

Table 3. Identified Issues and Recommendations for Riverside Pharmaceuticals Corp (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	We note the following statements: "Dispense in a tightly closed, light-resistant container. This is a bulk package and not intended for dispensing. (b) (4) .	The proposed closure ((b) (4)) is (b) (4) so the statement is incorrect.	We recommend you clarify whether you intend to use a (b) (4) closure. If not, remove those statements.
4.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the expiration date format from a medication safety perspective which may result in a risk for deteriorated drug medication errors.	Identify the expiration date 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. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM 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.

5 CONCLUSION

Our evaluation of the proposed carbidopa and levodopa PI and container label 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 Riverside Pharmaceuticals Corp so that 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 carbidopa and levodopa that Riverside Pharmaceuticals Corp submitted on October 14, 2020, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and carbidopa and levodopa		
Product Name	Sinemet	pending
Initial Approval Date	May 2, 1975	N/A
Active Ingredient	Carbidopa and levodopa	
Indication	Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication	
Route of Administration	Oral	
Dosage Form	Tablet	
Strength	25 mg/100 mg 10mg/100 mg 25 mg/250 mg	25 mg/100 mg: Tablets are functionally scored into 4 segments to facilitate precise dose fractionation; each segment contains carbidopa 6.25 mg and levodopa 25 mg.
Dose and Frequency	<u>Usual Initial Dose</u> 25 mg/100 mg three times a day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage of eight 25 mg/100 mg tablets a day is reached. <u>Maintenance Dose</u> Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided.	<u>Usual Initial Dose</u> 1 tablet three times a day. Dosage may be increased by one tablet once daily or every other day as necessary until a dosage of eight tablets a day is reached. <u>Maintenance therapy</u> As facilitated by functional scoring, therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 mg to 100 mg of carbidopa per day should be provided. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

	Experience with total daily dosages of carbidopa greater than 200 mg is limited. When a greater proportion of carbidopa is required, one tablet of SINEMET 25-100 may be substituted for each tablet of SINEMET 10-100. When more levodopa is required, SINEMET 25-250 should be substituted for SINEMET 25-100 or SINEMET 10-100. If necessary, the dosage of carbidopa and levodopa 25-250 may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day.	
How Supplied	Bottles containing 100 tablets	
Storage	Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.
Container Closure	HDPE bottle	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 27, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 214869. Our search did not identify any previous reviews.

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,[b] along with postmarket medication error data, we reviewed the following carbidopa and levodopa labels and labeling submitted by Riverside Pharmaceuticals Corp on October 14, 2020.

- Container label
- Prescribing Information (Image not shown) Available from: \\CDSESUB1\evsprod\nda214869\0001\m1\us\m1-14-labeling\m1-14-1-draft-label\m1-14-1-3-draft-label-text\1-14-1-3-draft-labeling-text.pdf

F.2 Label and Labeling Images

Container label

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

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