CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214869Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 214869
Review # 2

Drug Product Name	DHIVY (Carbidopa and Levodopa)
Dosage Form	Tablets
Strength	25 mg/100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Riverside Pharmaceuticals
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur [1]	Donna Christner
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Pratibha Bhat	Shujun Chen
Microbiology	N/A	
Biopharmaceutics	Kamrun Nahar	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	
Environmental	N/A	

[1] Adequate for Review #1 and no additional drug substance information submitted.

SUBMISSIONS REVIEWED IN REVIEW #2

Submission	Document Date	Discipline(s) Affected
SD-14, response to IR	6/30/3021	Drug product, manufacturing, biopharmaceutics
SD-16, response to IR **Major Amendment**	7/30/2021	Drug product, manufacturing, biopharmaceutics
SD-17, response to IR	8/12/2021	Manufacturing

SUBMISSIONS REVIEWED IN REVIEW #1

Submission	Document Date	Discipline(s) Affected
SD-001, original NDA	10/14/2020	All
SD-003, response to information request (IR)	12/7/2020	Manufacturing
SD-004, response to IR	12/30/2020	Manufacturing
SD-006, CMC amendment	2/12/2021	Manufacturing
SD-010, Response to IR	5/19/2021	Drug product, manufacturing, biopharmaceutics
SD-011, Response to IR	6/1/2021	Manufacturing

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

This addendum to the OPQ integrated review dated July 17, 2021 (Review #1) conveys the OPQ recommendation that the Agency **APPROVE** NDA 214869, DHIVY (carbidopa and levodopa) tablets. The current recommendation supersedes the previous OPQ recommendation that the Agency issue a complete response for the application. NDA 214869, as amended, provides adequate assurance the product will be suitable for use in the intended patient population.

II. SUMMARY OF QUALITY ASSESSMENTS

Background

In this 505(b)(2) NDA, the applicant seeks approval of an immediate release carbidopa and levodopa tablet in a single strength, 25 mg/100 mg. The only difference between the proposed product and the corresponding strength of the listed drug, Sinemet® tablets is the presence of three score lines that allow for dose adjustment in 6.25 mg/25 mg increments. The first OPQ Integrated Review[1] for the NDA recommended that a Complete Response Letter issue as the applicant had not fully responded to information requests (IRs) conveyed in the April 26, 2021 IR letter. Outstanding deficiencies were related to the drug product, manufacturing and biopharmaceutics. The deficiencies and their resolution are summarized below.

Drug Product: Adequate

The Applicant did not submit supplemental method validation data to support changes to the dissolution method, or photostability data in time for evaluation under Review #1. The information received in the July 30, 2021, amendment is adequate to support product quality.

Per Review #1, the proposed shelf-life of **24 months when stored at 20°C to 25°C** (68°F to 77° F) [USP controlled room temperature], is justified. This should be communicated in the final action letter.

Manufacturing: Adequate

Based on the physical, chemical, and microbial testing results submitted on July 30, 2021 and August 12, 2021, the bulk hold times for drug product (b) (4) and finished bulk product are acceptable.

[1] https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80602b6a&showAsPdf=true

All sites proposed for manufacture and testing Levodopa USP, Carbidopa USP and DHIVY (carbidopa and levodopa tablets) are currently acceptable. Facility status should be verified prior to final action on the NDA.

Biopharmaceutics: **Adequate**

The Applicant agreed to adopt the dissolution method recommended in the dissolution guidance[2] for immediate-release solid dosage forms containing highly soluble drug substances but did not provide the requested data in time for assessment in Review #1. Dissolution data of whole and split tablet segment A, B, C and D of carbidopa and levodopa tablets, 25 mg/100 mg showed very rapid release, >85% drug release within 15 minutes with low variability (b) (4) (b) (4) (b) (4) Therefore, the proposed dissolution method and acceptance criterion is deemed adequate.

[2] https://www.fda.gov/media/92988/download

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
Senior Product Quality Assessor for Neurology Products
Office of New Drug Products

10/15/2021

Martha Heimann

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QUALITY REVIEW

BIOPHARMACUTICS
NDA: NDA 214869
Drug Product Name / Strength: (b) (4) (Carbidopa 25 mg/Levodopa 100 mg) Tablet
Route of Administration: Oral
Applicant Name: Riverside Pharmaceuticals Corporation
Indication: Treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Submission date: 10/14/2020
Primary Reviewer: Kamrun Nahar, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.
Recommendation: **Adequate**

ADDENDUM:

This Biopharmaceutics Review Addendum provides updates to the overall assessment to the original Biopharmaceutics Review in Panorama dated July 06, 2021 in the following link: https://panorama.fda.gov/task/view?ID=5fdccc60002073e18f02977025840c8a. .

REVIEW SUMMARY:

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development. Summary of the key findings are presented below, based on the review of the provided information/data, including the Applicant's responses to the Information Request (IR):

1) Dissolution Method and Acceptance Criteria:

The Applicant originally proposed (b) (4) the Applicant used USP apparatus II (paddle). The Applicant did not investigate or provide information regarding suitability or discriminating ability of the proposed modified dissolution method.

In view of the claimed high aqueous solubility and low risk of these drug substances, the Applicant was requested to conduct additional dissolution tests using a recommended method in FDA dissolution Guidance for immediate-release solid dosage form drug product containing highly soluble drug substances (August 2018)[1]. The Applicant has adopted the Guidance-recommended dissolution method and provided dissolution profile data of the registration batches in the IR response. Dissolution data of whole and split tablet segments of the proposed product showed very rapid release (>85% drug release within 15 minutes), (b) (4)

[1] https://www.fda.gov/media/92988/download

2) Bridging of Formulations:

No bridging is needed because the Applicant used the final to-be-marketed product (batch# CD9FD01D28A) to conduct the pivotal bioavailability/bioequivalence study.

RECOMMENDATION:

Form a Biopharmaceutics perspective, NDA 214869 for (b) (4) (carbidopa/levodopa) tablets, 25mg/100 mg is **adequate** for approval.

Approved dissolution method and acceptance criterion for quality control and stability testing of the proposed (b) (4) (carbidopa/levodopa) tablets, 25mg/100 mg:

Apparatus	Rotation Speed (rpm)	Medium	Volume (mL)	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	50	0.1N HCl, pH 1.2	500	37±0.5°C	Q= (b) (4)% in 30 minutes

BIOPHARMACEUTICS ASSESSMENT:

List Submissions being reviewed:

1. 0001 10/14/2020 Original submission
2. 0010 05/19/2021 Response to FDA Information Request
3. 0014 06/30/2021 Response to FDA Information Request
4. 0016 07/30/2021 Response to FDA Information Request

Information Request (dated 04/26/2021):
\\CDSESUB1\evsprod\NDA214869\0014\m1\us\m1-11-info-amend-not-under-m2-5\m1-11-1-quality-info-amend

1. We request that you provide aqueous solubility data across physiologic pH condition (i.e., pH 1.2- pH 6.8) to support your claim that both carbidopa and levodopa are highly soluble compounds, i.e., BCS class I or 3 drug substance.
2. In view of the claimed high solubility for both carbidopa and levodopa, we do not find your use of (b) (4)-mL dissolution volume justified. Please refer to the FDA Guidance for Industry, "Dissolution testing and acceptance criteria for immediate-release solid oral dosage form products containing high solubility drug substances (April 2018)" for recommended dissolution method/test condition. We request that you generate full dissolution profile data of the pivotal clinical and primary registration batches (n=12) using 500 mL dissolution volumes and implement 500 mL instead for batch release and stability testing.
3. Provide information/data to demonstrate the conformity of drug release from the split tablets (i.e., for all the segments) in 500 mL dissolution volume to the proposed dissolution acceptance criterion set based on whole tablets

Applicant's Response 1 (dated 06/30/2021):
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In the response letter dated 06/30/2021, the Applicant provided solubility data of carbidopa and levodopa at three different pH conditions, i.e., pH 1.2, 4.5 and 6.8 at 37°C±1°C (Tables 1 and 2). Solubility data showed that both carbidopa and levodopa at the highest single therapeutic dose (carbidopa 25mg/levodopa 100 mg) is soluble in 250 mL of aqueous media of three pH 1.2, 4.5 and 6.8 conditions up to 24 hours except for the 24 hours' time points for carbidopa. Per the FDA/ICH M9 guidance[2], a drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 mL or less of aqueous media over the pH range of 1.2-6.8 at 37±1°C, while the solubility is maintained over relevant time frames to accommodate the expected duration of absorption. Considering that the maximum plasma concentration (Cmax) of carbidopa occurred at approximately 3 hours after oral administration of (b) (4) under fasted condition, this Reviewer does not expect the lower solubility of carbidopa at 24 hours will have significant impact on the pharmacokinetic property of carbidopa. This Reviewer

[2] https://www.fda.gov/media/148472/download

agrees that, based on the provided solubility data, both carbidopa and levodopa can be considered as highly soluble drug substances across the physiologic pH range 1.2-6.8.

Table 1: Solubility of Carbidopa in three buffers

Sample		30 minutes	1 hour	2 hours	4 hours	24 hours
pH 1.2 Buffer	V-1	0.1826	0.1832	0.1839	0.1892	0.2506
	V-2	0.1850	0.1862	0.1878	0.1926	0.2545
	V-3	0.1896	0.1913	0.1931	0.1982	0.2734
	Average	0.1857	0.1869	0.1883	0.1933	0.2595
pH 4.5 Buffer	V-1	0.1532	0.1607	0.1692	0.1735	0.1838
	V-2	0.1481	0.1569	0.1624	0.1680	0.1807
	V-3	0.1522	0.1629	0.1647	0.1693	0.1822
	Average	0.1511	0.1601	0.1654	0.1703	0.1823
pH 6.8 Buffer	V-1	0.1151	0.1324	0.1193	0.1027	0.0232
	V-2	0.1114	0.1316	0.1220	0.1045	0.0228
	V-3	0.1146	0.1350	0.1186	0.1061	0.0224
	Average	0.1137	0.1330	0.1200	0.1044	0.0228

Table 2: Solubility of Levodopa

Sample		30 minutes	1 hour	2 hours	4 hours	24 hours
pH 1.2 Buffer	V-1	0.9602	1.0154	1.0218	1.0403	1.2657
	V-2	0.9888	1.0221	1.0340	1.0505	1.3461
	V-3	0.9948	1.0271	1.0372	1.0601	1.3909
	Average	0.9813	1.0215	1.0310	1.0503	1.3342
pH 4.5 Buffer	V-1	0.8557	1.0188	1.0311	1.0454	1.2687
	V-2	0.6847	0.9717	1.0153	1.0401	1.2466
	V-3	0.8204	0.9829	1.0279	1.0505	1.2422
	Average	0.7869	0.9911	1.0248	1.0453	1.2525
pH 6.8 Buffer	V-1	0.5828	0.6642	1.0277	1.0964	1.4431
	V-2	0.6449	0.7195	0.8676	0.9812	1.1781
	V-3	0.6532	0.7539	0.8541	1.0042	1.1146
	Average	0.6269	0.7126	0.9165	1.0272	1.2453

Applicant's Responses 2 and 3 (dated 07/30/2021):
\\CDSESUB1\evsprod\nda214869\0016\m1\us\m1-11-info-amend-not-under-m2-5\m1-11-1-quality-info-amend\1-11-1-quality-info-amendment.pdf

The Applicant adopted the Guidance-recommended dissolution method and provided dissolution profile data of the registration batches in the IR response dated 07/30/2021 (Tables 3, 4, and 5). Dissolution data of whole and split tablet segments A, B, C and D of carbidopa and levodopa tablets showed very rapid release (>85% drug release within 15 minutes) with low variability (b) (4) (b) (4) (b) (4) Refer to the ***Appendix 1*** for the dissolution data of the individual vessel value.

Table 3: Dissolution data of carbidopa/ levodopa tablets, 25mg/100mg (lot#CD9FD01D28A)

Time Point	Percent Dissolved Carbidopa					Percent Dissolved Levodopa				
30 Min	W. Tab	Seg A	Seg B	Seg C	Seg D	W. Tab	Seg A	Seg B	Seg C	Seg D
Min.	(b) (4)									
Max.										
Mean of 12	96	92	93	92	95	96	97	97	99	101
Specification	Average of 12 units is equal to or greater than Q No Unit is less than Q- (b) (4) Q= (b) (4) % of Labeled amount of 25 mg of Carbidopa					Average of 12 units is equal to or greater than Q No Unit is less than Q- (b) (4) Q= (b) (4) % of Labeled amount of 100 mg of Levodopa				

Table 4: Dissolution data of carbidopa/levodopa tablets, 25mg/100mg (lot#CG9FD01E01)

Time Point	Percent Dissolved Carbidopa					Percent Dissolved Levodopa				
30 Min	W. Tab	Seg A	Seg B	Seg C	Seg D	W. Tab	Seg A	Seg B	Seg C	Seg D
Min.	(b) (4)									
Max.										
Mean of 12	96	91	92	94	92	96	94	96	97	95
Specification	Average of 12 units is equal to or greater than Q No Unit is less than Q- (b) (4) Q= (b) (4) % of Labeled amount of 25 mg of Carbidopa					Average of 12 units is equal to or greater than Q No Unit is less than Q- (b) (4) Q= (b) (4) % of Labeled amount of 100 mg of Levodopa				

Table 5: Dissolution data of carbidopa/levodopa tablets, 25mg/100mg (lot#CG9FD01E02)

Time Point	Percent Dissolved Carbidopa					Percent Dissolved Levodopa				
30 Min	W. Tab	Seg A	Seg B	Seg C	Seg D	W. Tab	Seg A	Seg B	Seg C	Seg D
Min.	(b) (4)									
Max.										
Mean of 12	97	90	93	94	94	97	94	99	98	97
Specification	Average of 12 units is equal to or greater than Q No Unit is less than Q (b) (4) Q= (b) (4) % of Labeled amount of 25 mg of Carbidopa					Average of 12 units is equal to or greater than Q No Unit is less than Q- (b) (4) Q= (b) (4) % of Labeled amount of 100 mg of Levodopa				

Appendix 1. Dissolution Data

Dissolution data: \\CDSESUB1\evsprod\nda214869\0016\m3\32-body-data\32p-drug-prod\32p-(b) (4)-ccu\32p5-contr-drug-prod\32p54-batch-analyses\vp-859-dissolution-summary-report.pdf

Kamrun Nahar

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Ta-Chen Wu

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Complete Response

NDA 214869
Review # 1

Drug Product Name	DHIVY (Carbidopa and Levodopa)
Dosage Form	Tablets
Strength	25 mg/100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Riverside Pharmaceuticals
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Pratibha Bhat	Shujun Chen
Microbiology	N/A	
Biopharmaceutics	Kamrun Nahar	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	
Environmental	N/A	

SUBMISSIONS REVIEWED

Submission	Document Date	Discipline(s) Affected
SD-001, original NDA	10/14/2020	All
SD-003, response to information request (IR)	12/7/2020	Manufacturing
SD-004, response to IR	12/30/2020	Manufacturing
SD-006, CMC amendment	2/12/2021	Manufacturing

SD-010, Response to IR	5/19/2021	Drug product, manufacturing, biopharmaceutics
SD-011, Response to IR		Manufacturing

SUBMISSIONS DEFERRED

Submission	Document Date	Discipline(s) Affected
SD-14, response to IR	6/30/3021	Drug product, manufacturing, biopharmaceutics

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II		(b) (4)	Adequate	4/22/2021	Reviewed by G. Ladouceur
	II			Adequate	11/20/2020	Reviewed by G. Ladouceur
	III			NR [1]	--	
	III			NR	--	
	III			NR	--	
	III			NR	--	
	III			NR	--	
	III			NR	--	
	III			NR	--	

[1] Not reviewed. Adequate information was provided in NDA.

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

Document	Application Number	Description
NDA	17555	Approved application for Sinemet® tablets referenced under 505(b)(2) to support safety and efficacy of carbidopa and levodopa. NDA 17555 was recently transferred from Merck, Sharp & Dohme to Organon, Inc.
IND	135441	Development of Riverside scored formulation

2. CONSULTS

None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends that a **Complete Response** letter be issued for NDA 214869, DHIVY (carbidopa and levodopa) tablets. Although several deficiencies were addressed by the applicant during the review cycle, the remaining have not been fully addressed.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Levodopa was initially approved for treatment of Parkinson's disease in 1970. The therapeutic activity of levodopa is due to its conversion by DOPA decarboxylase to dopamine in the CNS. Carbidopa has no therapeutic effect on its own. Instead, carbidopa enhances the therapeutic effect of levodopa by inhibiting peripheral conversion of levodopa to dopamine; thus, increasing CNS exposure to levodopa and dopamine. Merck, Sharp & Dohme developed the first product containing both levodopa and carbidopa, Sinemet tablets, which were approved in 1975 (NDA 17555). Currently, there are multiple approved dosage forms containing both carbidopa and levodopa. Single entity products containing either carbidopa or levodopa are also available.

The applicant, Riverside Pharmaceuticals, is seeking approval under 505(b)(2) for a new carbidopa and levodopa fixed dose combination tablet. The applicant references NDA 17555 for Sinemet® (carbidopa and levodopa) tablets to support safety and efficacy of carbidopa and levodopa for treatment of Parkinson's disease. Unlike Sinemet tablets, which are available in 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg carbidopa/levodopa (CD/LD) strengths, the applicant intends to market a single tablet strength containing 25 mg/100 mg CD/LD with multiple score lines.

In the initial risk assessment, content uniformity (whole tablet) and scored tablet functionality (uniformity, dissolution and friability) were considered moderate risk critical quality attributes (CQAs) considered moderate risk include. The remaining CQAs, including assay, stability, dissolution (whole tablet) and microbial limits were considered low risk.

Proposed indication(s) including intended patient population	Treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.
Duration of treatment	Chronic
Maximum daily dose	Levodopa: 800 mg [1]

	Carbidopa: 200 mg
Alternative methods of administration	None

[1] Although levodopa doses up to 2000 mg/day are approved, the maximum levodopa dose that could be achieved with the proposed product is limited by carbidopa.

B. Quality Assessment Overview

Drug Substances: Adequate

Carbidopa USP and Levodopa USP drug substances are manufactured by (b) (4) (b) (4) Information to support manufacture and control of carbidopa is cross-referenced to (b) (4) DMF (b) (4). The DMF was last reviewed on 04/22/2021 and deemed adequate. Information to support manufacture and control of levodopa is cross-referenced to (b) (4) DMF (b) (4). The DMF was reviewed on 11/20/2020 and deemed adequate. (b) (4) assigns a (b) (4)-month retest date for both carbidopa and levodopa.

The applicant provided general information, acceptance specifications, and certificates of analysis for carbidopa and levodopa in the NDA. The information provided in the NDA is consistent with information in the respective DMFs and adequate to support approval.

Drug Product: Inadequate

The proposed product is a (b) (4) triple-scored, immediate-release tablet containing 25 mg carbidopa and 100 mg levodopa. (b) (4) The individual segments can be separated by breaking along the score lines to achieve 6.25 mg/25 mg, 12.5 mg/50 mg, or 18.75 mg/75 mg CD/LD doses. The inactive ingredients are compendial excipients and their maximum daily exposures are comparable to or lower than other approved products. The product meets all requirements for functionally scored tablets.[1] The tablets are packaged in 100-count HDPE bottle with (b) (4) closures and (b) (4) The container closure system is suitable for pharmaceutical use and available stability data show that it provides adequate protection for the drug product through the proposed shelf-life.

The proposed specification, including the acceptance criteria for impurities, meets the USP monograph for Carbidopa and Levodopa Tablets. With the exception of the dissolution test, the proposed tests and acceptance criteria are appropriate to control the quality of this solid oral dosage form and all non-compendial methods are validated. The applicant has provided risk assessment in accordance with ICH

[1] Guidance for Industry, Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation

Q3D[2] to support the omission of test for elemental impurities. With respect to the dissolution test, the Biopharmaceutics reviewer has asked the applicant to change the dissolution medium volume from (b) (4) mL to 500 mL.[3] Submission of supporting documentation and data, including supplemental validation data for the HPLC method to be used in the revised dissolution testing are still pending. These data are not expected to be submitted until 7/30/2021.

The applicant provided up to 12 months of long-term and up to 6 months of accelerated stability data for the three primary stability batches. No trending was noted for both the whole and split tablets at both the storage conditions. The proposed shelf-life of 24 months, when stored at 20°C to 25°C (68°F to 77° F) [USP controlled room temperature], is supported by the data. However due to the unaddressed deficiencies, a shelf-life will not be granted at this time.

Labeling: Adequate

There are no outstanding labeling deficiencies.

Manufacturing: Inadequate

Carbidopa and levodopa 25 mg/100 mg tablets are manufactured using (b) (4) (b) (4) . CQAs for the tablets include identity, assay, BU, uniformity of dosage units, degradation products, dissolution, and appearance.

The proposed commercial batch size for carbidopa and levodopa tablets 25 mg/100 mg is same as that of the registration batch size, i.e. (b) (4) tablets. The equipment to be used for commercial batches has the same design and operating principles as the equipment used for the registration batches and there are no differences between the manufacturing processes clinical and commercial batches. In process controls and acceptance criteria are either maintained the same as that of registration batches or tightened for better control.

The applicant has addressed most of the process deficiencies identified during the review; however, data from hold time studies have not been submitted and are not expected until 7/30/2021.

All sites proposed for manufacture and testing Levodopa USP, Carbidopa USP and DHIVY (carbidopa and levodopa tablets) are currently acceptable. Facility status should be verified prior to final action on the NDA.

[2] Elemental Impurities in Drug Products Guidance for Industry
[3] Biopharmaceutics review by Kamrun Nahar, 7/6/2021

Biopharmaceutics: Inadequate

The adequacy of the information and data submitted to support: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development was evaluated.

(b) (4)

the Applicant used USP apparatus II (paddle). The proposed dissolution method and acceptance criterion for quality control and stability testing of the proposed drug product are presented in the table below. The applicant's proposed a dissolution acceptance criterion of "Q= (b) (4)% in 30 minutes" as quality control for batch release and stability testing of the proposed drug product. The Applicant did not investigate or provide information regarding discriminating ability of the proposed modified dissolution method.

Apparatus	Rotation Speed (rpm)	Medium	Volume (mL)	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	50	0.1N HCl, pH 1.2	(b) (4)	37±0.5°C	Q= (b) (4)% in 30 minutes

In view of the claimed high aqueous solubility and low risk of these drug substances, the Applicant was requested to conduct dissolution test using a recommended method in the dissolution guidance[4] for immediate-release solid dosage forms containing highly soluble drug substances. The Applicant agreed to adopt the recommended method but did not provide the requested data in time for assessment. Therefore, the adequacy and acceptability of the dissolution method and acceptance criterion cannot be determined in this review cycle.

No formulation bridging is needed because the applicant used the final to-be-marketed product (Batch No. CD9FD01D28A) in the pivotal bioavailability/ bioequivalence study.

Environmental: Adequate

The Applicant claims a categorical exclusion per 21 CFR 25.31(a) and states that, pursuant to 21 CFR 25.15(d), no extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

[4] Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances Guidance for Industry (August 2018)

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay, stability	Formulation, raw materials, (b) (4), process parameters	**Low**	Selection of formulation, manufacturing parameter. Stability demonstrated in registration stability studies. However, the applicant has not provided data to support hold times for bulk product or data from (b) (4) studies on bulk and packaged tablets.	**Inadequate**	
Content uniformity	API physical characteristics, formulation, raw materials, (b) (4), process parameters	**Moderate**	The primary registration batches met CU criteria and the process parameters adequate to control the CU.	**Adequate**	
Physical stability (solid state)	API physical characteristics, formulation, raw materials, (b) (4), process parameters	**Low**		**Adequate**	
Dissolution – BCS Class I & III	API physical characteristics, formulation, raw materials, (b) (4), process parameters	**Low**	The sponsor has not finalized the dissolution method or submitted dissolution profiles generated using revised method.	**Inadequate**	
<u>Scored tablet</u>: Dissolution, BCS I/III Content uniformity (uneven split) (b) (4)	API physical characteristics, formulation, raw materials, (b) (4), process parameters	**Moderate**	Tablets meet all required tests to support labeling as functionally scored tablets.	**Adequate**	
(b) (4)		**Low**			
Microbial limits	Formulation, raw materials, (b) (4), container closure	**Low**		**Adequate**	

D. List of Deficiencies for Complete Response

Note: Final language depends on when information to be submitted is received.

The deficiencies listed below, which were previously conveyed in the April 26, 2021 Information Request Letter, have not been fully addressed. We acknowledge the amendment(s) dated June 30, 2021 (and July 30, 2021). You may reference these amendments as part of your response.

Drug Substance Deficiencies

N/A

Drug Product Deficiencies

1. Provide ICH photostability data conducted in accordance with ICH Q1E Guideline.

2. Because the tablets are (b) (4) scored, they are (b) (4) (b) (4)

Labeling Deficiencies

N/A

Manufacturing Deficiencies

3. Provide the holding time (b) (4) (b) (4) supported by hold time study data. Also submit your Hold Time Study Protocol and Report.

   We acknowledge that you have provided "Bulk Hold Time Study Protocol-VP-855" and it is acceptable. However, you have not provided the "Bulk Hold Time Study Report". Submit your "Bulk Hold Time Study Report".

Biopharmaceutics Deficiencies

4. We request that you provide aqueous solubility data across physiologic pH condition (i.e. pH 1.2- pH 6.8) to support your claim that both carbidopa and levodopa are highly soluble compounds, i.e., BCS class I or 3 drug substance.

5. In view of the claimed high solubility for both carbidopa and levodopa, we do not find your use of (b) (4)-mL dissolution volume justified. Please refer to the FDA Guidance for Industry, "Dissolution testing and acceptance criteria for immediate-release solid oral dosage form products containing high solubility drug substances (April 2018)" for recommended dissolution method/test condition.

We request that you generate full dissolution profile data of the pivotal clinical and primary registration batches (n=12) using 500 mL dissolution volumes and implement 500 mL instead for batch release and stability testing.

6. Provide information/data to demonstrate the conformity of drug release from the split tablets (i.e., for all the segments) in 500 mL dissolution volume to the proposed dissolution acceptance criterion set based on whole tablets.

In addition to the deficiencies listed above, provide supplemental validation data for the HPLC method to be used in the revised dissolution test.

Microbiology Deficiencies

N/A

Other Deficiencies (Specify discipline, such as Environmental)

N/A

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
CMC Lead for Neurology Products
Office of New Drug Products

7/15/2021

Martha Heimann

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	Adequate Note: The tradename will need to be revised to DHIVY
Established name(s)	carbidopa and levodopa	adequate
Route(s) of administration	Oral	adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablet: Carbidopa and levodopa 25 mg/100 mg	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Functionally scored	Meets the criteria for "functionally scored"
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

1.2 FULL PRESCRIBING INFORMATION

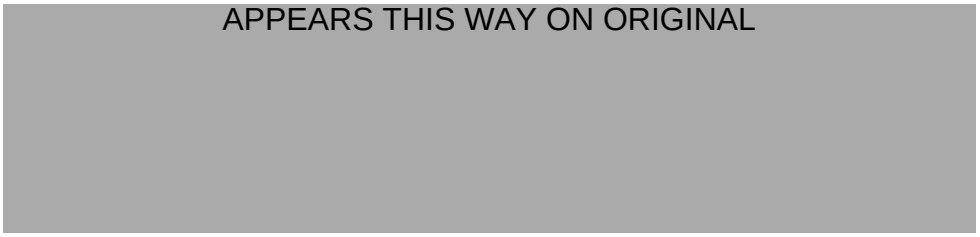
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	n/a	n/a

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	adequate
Strength(s) in metric system	25 mg of carbidopa and 100 mg of levodopa	adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	n/a
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	white to off-white tablets with functional scoring	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Functionally scored tablets	Meets the criteria for "functionally scored"
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

1.2.3 Section 11 (DESCRIPTION)



Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	Adequate Note: The tradename will need to be revised to DHIVY
Dosage form(s) and route(s) of administration	Tablets for oral administration	adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	n/a
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Statement of being sterile (if applicable)	n/a	n/a
Pharmacological/ therapeutic class	Yes	adequate
Chemical name, structural formula, molecular weight	Yes	adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	Yes	adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	n/a
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	n/a

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	adequate
Strength(s) in metric system	25 mg of carbidopa and 100 mg of levodopa	adequate
Available units (e.g., bottles of 100 tablets)	bottles of 100	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white tablets with functional scoring	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	"functional scoring"	Meets the requirement of "functionally scored"
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store in a tightly closed container, protected from light and moisture.	The product is light sensitive
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	n/a	n/a
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	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)	adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	n/a
Include information about child-resistant packaging	Not listed as child resistant	(b) (4)

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Riverside Pharmaceuticals Corporation Washington, DC 20006, USA	adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling

n/a

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Dhivy Carbidopa/Levodopa	adequate
Dosage strength	25 mg/100 mg	adequate
Route of administration	n/a	ROA not required for oral dosage forms
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	n/a
Net contents (e.g. tablet count)	100 tablets	adequate
"Rx only" displayed on the principal display	Yes	adequate
NDC number	NDA 77334-701-01	adequate
Lot number and expiration date	Yes	adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Stored at 20°C – 25°C (68°F – 77°F); excursion permitted to 15°C – 30°C (59°F – 86°F). [See USP Controlled Room Temperature]	adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	n/a
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	n/a

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Bar code	Yes	adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4) Riverside Pharmaceuticals Corporation Washington, DC 20006, USA	adequate
Medication Guide (if applicable)	n/a	n/a
No text on Ferrule and Cap overseal	n/a	n/a
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	n/a
And others, if space is available	n/a	n/a

Assessment of Carton and Container Labeling: ***Adequate/***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name: Mariappan V. Chelliah
Secondary Assessor Name: Julia Pinto

Mariappan Chelliah

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Julia Pinto

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QUALITY REVIEW

BIOPHARMACUTICS
NDA: NDA 214869
Drug Product Name / Strength: (b) (4) (Carbidopa 25 mg/Levodopa 100 mg) Tablet
Route of Administration: Oral
Applicant Name: Riverside Pharmaceuticals Corporation
Indication: Treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Submission date: 10/14/2020
Primary Reviewer: Kamrun Nahar, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.
Recommendation: **Inadequate**

BACKGROUND:

The Applicant is seeking approval under 505(b)(2) regulatory pathway for (b) (4) (carbidopa / levodopa) immediate-relese tablet, 25mg/100 mg, for oral administration, indicating for the Treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. The listed drug is Sinemet® (NDA# 17555) held by MERCK SHARP AND DOHME CORP.

REVIEW SUMMARY:

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development. Summary of the key findings are presented below, based on the review of the provided information/data:

1) Dissolution Method and Acceptance Criteria:

(b) (4)

the Applicant used USP apparatus II (paddle). The proposed dissolution method and acceptance criterion for quality control and stability testing of the proposed drug product are presented in the table below. The Applicant's proposed a dissolution acceptance criterion of "Q= (b) (4) % in 30 minutes" as quality control for batch release and stability testing of the proposed drug product. The Applicant did not investigate or provide information regarding discriminating ability of the proposed modified dissolution method.

In view of the claimed high aqueous solubility and low risk of these drug substances, the Applicant was requested to conduct dissolution test using a recommended method in FDA dissolution Guidance for immediate-release solid dosage form drug product containing highly soluble drug substances (August 2018)[1]. The Applicant agreed to adopt the Guidance-recommended method but did not provide the requested data in time for assessment. Therefore, the adequacy and acceptability of the dissolution method and acceptance criterion cannot be determined in this review cycle.

[1] https://www.fda.gov/media/92988/download

The originally proposed dissolution method and acceptance criterion for quality control and stability testing of the proposed (b) (4) (carbidopa/levodopa) tablets, 25mg/100 mg:

Apparatus	Rotation Speed (rpm)	Medium	Volume (mL)	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	50	0.1N HCl, pH 1.2	(b) (4)	37±0.5°C	Q= (b) % in 30 minutes

2) Bridging of Formulations:

No bridging is needed because the Applicant used the final to-be-marketed product (batch# CD9FD01D28A) to conduct the pivotal bioavailability/bioequivalence study.

CONCLUSION AND RECOMMENDATION:

The Applicant did not provide adequate responses with the necessary information and dissolution data in time for the assessment during the review cycle. Form a Biopharmaceutics perspective, NDA 214869 for (b) (4) (carbidopa/levodopa) tablets, 25mg/100 mg is **inadequate** for approval.

BIOPHARMACEUTICS ASSESSMENT:

List Submissions being reviewed:

1. 0001 10/14/2020 Original submission
2. 0010 05/19/2021 Response to FDA Information Request
3. 0014 06/30/2021 Response to FDA Information Request

Highlight Key Outstanding Issues from Last Cycle: None

I. Solubility Per Biopharmaceutical Classification System (BCS):

The Applicant claimed that both Carbidopa and Levodopa are highly soluble compound (i.e., BCS Class I or III). However, the Applicant did not provide solubility data of the drug substances. Hence, the Applicant was requested to provide aqueous solubility information. In the response to the Information request (IR) dated 04/26/2021, the Applicant stated that they will provide solubility data on 06/30/2021. On 06/30/2021, the Applicant provided a report VR-857 containing results of the study demonstrated that both carbidopa and levodopa are considered highly soluble per the BCS criteria. This late Amendment could not be evaluated in time for this review cycle.

II. Dosage Form:

The proposed drug product, (b) (4) (carbidopa/levodopa) Tablet, 25mg/100 mg, manufactured by (b) (4), is a (b) (4) tablet that consists of the active ingredients, carbidopa (25 mg) and levodopa (100 mg), along with the excipients (b) (4) (Figure 1 and Table 1). (b) (4) (b) (4). The tablets have three (b) (4) scoring that helps to break the tablet to provide dose-fraction thus the tablet can be used as whole or divided into carbidopa 6.25mg/levodopa 25 mg, carbidopa 12 mg/levodopa 50 mg or carbidopa 18.75mg/levodopa 75 mg.

Figure 1. Proposed (b) (4) (carbidopa/levodopa) Tablet, 25mg/100 mg ((b) (4))

a. Schematic representation of a carbidopa/levodopa tablet

b. Final commercial carbidopa/levodopa Tablet

Table 1. a. Components of the (b) (4)

(b) (4)

III. Dissolution Method:

The Applicant claimed that both carbidopa and levodopa are highly soluble compound as per BCS classification, i.e., BCS class I or III. (b) (4)

the Applicant used USP apparatus II (paddle) (b) (4)

The Applicant's proposed dissolution method is as follows: USP apparatus II, 50 rpm, 0.1N HCl (pH 1.2), (b) (4) mL at 37±0.5°C (see Table 2). As stated by the Applicant, the proposed dissolution method condition is same as the FDA guidance (August 2018) dissolution method except for the dissolution medium volume, i.e., FDA guidance method recommends 500 mL volume and the Applicant used (b) (4) mL of medium volume. Note that the dissolution profile data assessed and presented in this review (APPENDIX 1) are generated by the proposed modified method.

Table 2. Proposed dissolution method and acceptance criterion of (b) (4) (carbidopa/levodopa) tablets, 25mg/100mg

Apparatus	Rotation Speed (rpm)	Medium	Volume (mL)	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	50	0.1N HCl	(b) (4)	37±0.5°C	Q= (b) (4)% in 30 minutes

In view of the claimed high aqueous solubility and low risk of these drug substances, the Applicant was requested to provide dissolution data using a recommended FDA guidance method for drug substance with high solubility (IR dated 04/26/2021). The Applicant did not provide the adequate response to provide the requested data in time for a thorough assessment, hence this Reviewer is unable to determine the adequacy of the dissolution method.

Dissolution Acceptance Criterion:

The Applicant provided dissolution profile data of the whole tablets in three physiologically relevant pH conditions, i.e., in 0.1N HCl (pH 1.2), pH 4.5 buffer, and pH 6.8 buffer media. As illustrated in Figure 2, drug release rates of the carbidopa and levodopa are similar in 0.1N HCl and buffer medium pH 4.5. However, in pH 6.8 medium, dissolution of carbidopa was reported to be over 100% by 60 minutes, while drug release was not complete for levodopa up to 60 minutes. However, >85% release occurred in three media at 30 minutes time points. Individual data generated in 0.1N HCl pH 1.2 dissolution medium are presented in Tables 3~4.

The Applicant proposed dissolution acceptance criterion as "Q= (b) (4)% in 30 minutes" based on the dissolution data (b) (4) Note that no investigation of discriminating ability of the proposed modified dissolution method was performed or provided.

Figure 2. Dissolution profiles of carbidopa and levodopa at various pH of the dissolution media from carbidopa/levodopa tablets, 25 mg/100mg using the QC dissolution method

a. Carbidopa

b. Levodopa

(b) (4)

Table 3. Dissolution profile data of carbidopa/levodopa tablets, 25 mg/100 mg, in 0.1N HCl

Time Point	10 min		15 min		30 min		45 min		60 min	
Vessel No.	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Min(n=1-12)										
Max(n=1-12)										
Avg(n=1-12)	90	91	94	95	97	97	98	98	99	98

Table 4. Dissolution profile data of carbidopa/levodopa tablets, 25mg/100mg in buffer medium pH 4.5

Time Point	10 min		15 min		30 min		45 min		60 min	
Vessel No.	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Min(n=1-12)										
Max(n=1-12)										
Avg(n=1-12)	76	80	85	88	90	93	93	95	94	96

Table 5. Dissolution profile data of carbidopa/levodopa tablets, 25mg/100mg in buffer medium pH 6.8

Time Point	10 min		15 min		30 min		45 min		60 min	
Vessel No.	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)	Levodopa (%)	Carbidopa (%)
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Min(n=1-12)										
Max(n=1-12)										
Avg(n=1-12)	78	85	84	93	89	99	92	102	93	104

Split tablets dissolution data:

The Applicant conducted dissolution testing for split tablet drug release from carbidopa/levodopa tablets, 25mg/100mg, clinical lot# CD9FD01D28, i.e., segment A, B, C and D, splitted both manually and mechanically using the proposed dissolution method at 30 minutes time-point. As shown in Table 6 and Table 7, drug releases of both drug substances from all four segments of carbidopa/levodopa tablets splitted mechanically and manually achieved >85% of the drug release at 30 minutes time-point and confirmed to the proposed acceptance criterion.

Table 6. Dissolution data of carbidopa/levodopa tablets, lot# CD9FD01D28 (manual splitting)

Product	(b) (4) (Carbidopa 25 mg & Levodopa 100 mg) Tablets						Lot CD9FD01D28	
	Segment A		Segment B		Segment C		Segment D	
Sample	%LC	%LC	%LC	%LC	%LC	%LC	%LC	%LC
	Carbidopa	Levodopa	Carbidopa	Levodopa	Carbidopa	Levodopa	Carbidopa	Levodopa
1	(b) (4)							
2								
3								
4								
5								
6								
7#								
8								
9								
10								
11								
12								
13								
14								
15								
Average	92.8	95.1	94.9	97.2	97.2	99.6	97.6	100.0
Min.	(b) (4)							
Max								
AV†	10.8	8.5	8.2	6.3	8.5	7.2	14.5	14.2

Highlighted data is (b) (4) Tablet units; Refer Approved QC copy of COA report attachment.

Table 7. Dissolution data of carbidopa/levodopa tablets, lot# CD9FD01D28 (mechanical splitting)

Product	(b) (4) (Carbidopa 25 mg & Levodopa 100 mg) Tablets						Lot CD9FD01D28	
	Segment A		Segment B		Segment C		Segment D	
Sample	%LC	%LC	%LC	%LC	%LC	%LC	%LC	%LC
	Carbidopa	Levodopa	Carbidopa	Levodopa	Carbidopa	Levodopa	Carbidopa	Levodopa
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15#								
Average	92.9	94.8	94.2	96.2	96.3	98.5	94.3	96.4
Min.	(b) (4)							
Max								
AV†	11.0	9.4	10.4	8.3	7.5	5.5	13.3	11.1

In view of both drug substances being highly soluble compounds, this Reviewer requested that the Applicant provide dissolution profile data of the clinical and registration batches generated using a suitable method recommended in the FDA's Guidance (August 2018) for oral solid dosage form containing highly soluble drug substance. The Applicant agreed to adopt the recommended method and provide data (IR response dated 06/30/2021) but did not provide the

requested data in time for a thorough assessment. Therefore, the adequacy and acceptability of the dissolution method and acceptance criterion cannot be determined during the review cycle.

V. Formulation Bridging:

The Applicant used a single lot of carbidopa/levodopa tablets, 25mg/100mg, lot# CD9FD01D28 to conduct the pivotal in vivo bioavailability (BA)/bioequivalence (BE) study (Study 190051). Since the clinical formulation is same as the to-be-marketed (TBM) formulation, no additional formulation bridging is required.

VI. Biowaiver:

The proposed product has only one strength, thus, no biowaiver request was submitted.

Appendix 1. Dissolution Data

1. Dissolution data of whole tablets: \\CDSESUB1\evsprod\nda214869\0001\m3\32-body-data\32p-drug-prod\32p-(b) (4)ccu\32p2-pharm-dev\vp-735-prot-and-results.pdf

2. Dissolution data of split tablets: \\CDSESUB1\evsprod\nda214869\0001\m3\32-body-data\32p-drug-prod\32p-(b) (4)ccu\32p2-pharm-dev\vr-702-segment-study.pdf

(b) (4)

Ta-Chen Wu

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Kamrun Nahar

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MARTHA R HEIMANN
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