CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214869Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	August 13, 2021
From	Natalie Getzoff, MD Teresa Buracchio, MD
Subject	Summary Memo
NDA/BLA # and Supplement #	214869
Applicant	Riverside Pharmaceuticals
Date of Submission	October 14, 2020
PDUFA Goal Date	August 14, 2021 (extended to November 14, 2021 after a Major Amendment)
Proprietary Name / Non-Proprietary Name	Dhivy (carbidopa/levodopa)
Dosage Form(s) / Strengths	carbidopa 25 mg/levodopa 100 mg immediate release tablets
Applicant Proposed Indication(s)/Population(s)	*Treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication*
Action or Recommended Action:	Approval

1. Background

The applicant has submitted a New Drug Application (NDA) for Dhivy (carbidopa 25 mg/ levodopa 100 mg) immediate release tablets. The applicant is seeking approval through the 505(b)(2) regulatory pathway and is relying on the findings of safety and effectiveness for the listed drug, Sinemet® 25 mg/100 mg, and on data from a relative bioavailability study for establishing a pharmacokinetic (PK) bridge between Dhivy to the listed drug. Sinemet tablets are available in 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg carbidopa/levodopa (CD/LD) strengths. However, the applicant intends to market a single tablet strength containing 25 mg/100 mg CD/LD with multiple score lines, allowing a ¼, ½, and ¾ split of the tablet.

Sinemet 25 mg/100 mg oral tablet was approved on May 22, 1974 (NDA 17555) and is currently indicated for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. The applicant proposes the same indication as Sinemet 25 mg/100 mg. The recommended starting dose for Sinemet 25 mg/100 mg is 1 tablet three times daily with a recommended maximum dosage of 2 tablets four times daily, taken orally. A Dhivy (25 mg/100 mg)tablet will provide an equivalent dose of the Sinemet 25 mg/100 mg tablet. The addition of ¼ and ¾ functional scoring to the tablet required that this be submitted under a 505(b)(2), not under Subpart D (505(j)).

2. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

According to the OPQ review, the drug substance is produced with adequate quality for use in the tablet formulation. The initial OPQ review identified a number of deficiencies that were outstanding on the OPQ due date of July 6, 2021. OPQ sent a Cumulative Information Request (IR) to the applicant on April 26, 2021, noting that response to the IR was necessary by June 8, 2021 to allow for adequate review time. On May 19, 2021, the applicant responded that the requested testing data would be submitted on June 30, 2021 and July 30, 2021. Although these responses were received after the stated due date, the information submitted in the June 30 and July 30 responses were deemed by OPQ to be adequate for a Major Amendment.

The drug product consists of a (b) (4), triple-scored, immediate-release tablet containing 25 mg carbidopa and 100 mg levodopa. 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 product is supplied in a 100-count HDPE bottle with (b) (4) (b) (4).

Stability and release testing were found to be acceptable. The stability data provides adequate support for a shelf-life of 24 months at USP Controlled Room Temperature. OPQ determined that the manufacturing process for the drug product appears to be satisfactory based on its process selection, in-process controls, final product release test, and executed submission batch records. All manufacturing facilities for this product were found to be acceptable. There were no outstanding issues identified in the OPQ review.

OPQ recommends approval.

3. Nonclinical Pharmacology/Toxicology

There were no nonclinical data included in the submission. The applicant is relying on nonclinical data from the listed drug.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewer Dr. Srinivas Rao Chennamaneni, with Team Leader Dr. Bilal AbuAsal.

A Phase 1, open-label, pharmacokinetic study (190051) that compared the bioavailability of CD/LD 25 mg/100 mg tablet (Dhivy) to a CD/LD 25 mg/100 mg tablet (FDA Approved Generic Reference) in healthy subjects served as the pivotal study for the application. The study also evaluated food effects.

Study 190051 consisted of three parts:

- Part I of the study compared, in a crossover study design, CD/LD 25 mg/100 mg oral tablet (FDA Approved Generic Reference) to the test drug Dhivy 25 mg/100 mg oral tablet in 45 healthy volunteers. The effect of food was also assessed.

- In Parts II and III, this study evaluated the effect of the LD dose-interval on its plasma PK profile in healthy volunteers. In Part II subjects were given 1 Dhivy tablet (CD/LD 25/100 mg) at 0 and 4 hours post-first dose and subjects in Part III were administered ½ Dhivy tablet (CD/LD 12.5/50 mg) at 0, 2, 4, and 6 hours post-first dose (total 50/200 mg in both parts).

Bioequivalence Assessment

The following table from the clinical study report for Study 190051 provides a summary of the comparative bioavailability data from the pivotal bioequivalence study.

Levodopa				
Parameter (units)	**Test**	**Reference**	**Geometric Mean Ratio (%)**	**90% Confidence Interval**
Cmax (ng/mL)	1062.12	1129.95	94.0	85.02 - 103.92
AUC0-t (ng*hr/mL)	2121.40	2213.45	95.84	93.50 - 98.25
AUC0-inf (ng*hr/mL)	2144.04	2235.15	95.92	93.60 - 98.31
Carbidopa				
Parameter (units)	**Test**	**Reference**	**Geometric Mean Ratio (%)**	**90% Confidence Interval**
Cmax (ng/mL)	125.38	123.80	101.28	95.44 - 107.47
AUC0-t (ng*hr/mL)	612.41	622.61	98.36	93.55 - 103.41
AUC0-inf (ng*hr/mL)	616.82	626.89	98.39	93.62 - 103.41

(Source: Clinical Study Report 190051 pages 64, and 69 In-Text Table 11.4.2.3

The results show that the geometric mean ratios for Cmax, AUC_{0-t}, and AUC_{0-inf} with the 90% CI of levodopa were approximately: 94% (85.02 - 103.92), 96% (93.50 - 98.25), and 96%, (93.60 - 98.31), respectively. For carbidopa, the geometric mean ratios for Cmax, AUC_{0-t}, and AUC_{0-inf} with the 90% CI were approximately: 101% (95.44 - 107.47), 98% (93.55 - 103.41), and 98%, (93.62 - 103.41), respectively. The results indicate similar rate and extent of CD/LD absorption after single dose of the test and reference products. The 90% confidence intervals are within the 80.0 to 125% range, acceptable boundaries for bioequivalence for both carbidopa and levodopa.

Food Effect

Food effect for Dhivy was assessed in a fasted state and after a high-fat meal as a part of the bioequivalence study. Although administration of Dhivy after a high-fat meal did not affect total exposure (AUC) for levodopa, the peak exposure (Cmax) was decreased by approximately 24% and delayed by 30 minutes. For carbidopa, the AUC and Cmax decreased significantly (64% and 60%, respectively) and Tmax occurred 1.0 hour earlier when Dhivy was administered after a high-fat meal.

As noted by OCP, the effect of food on the exposure of CD/LD was not described in the USPI for Sinemet. The review team conducted a cross study comparison using the data for Sinemet from previously approved generic products (ANDAs 074260 and 090324). In these products, the BE study was conducted under fed and fasted conditions allowing for evaluation of Sinemet under fed and fasted conditions. The effect of food on CD/LD exposure in Dhivy was comparable to food effect observed for Sinemet in the BE studies for ANDAs 074260 and 090324.

Effect of Dose Interval on Plasma PK of LD and CD

The effect of the LD dose-interval on its plasma PK profile was assessed in healthy volunteers in Parts II and III of Study 190051. The PK characteristics of ½ tablet of Dhivy (CD/LD 12.5/50 mg) given every 2 hours at 0, 2, 4, and 6 hours post-dose (Part III) were compared to the PK characteristics of one tablet of Dhivy (CD/LD 25/100 mg) given every 4 hours (Part II) over a period of 8.0 hours, to simulate standard SINEMET dosing.

LD exposure (AUC_{0-t}) was similar after administration of Dhivy 12.5/50 mg q2hr compared to Dhivy 25/100 mg q4hr. Time to peak concentration after one dose was also similar after administration of Dhivy 12.5/50 mg q2hr compared to Dhivy 25/100 mg q4hr. When 12.5/50 mg every 2 hours dosing was compared to 25/100 mg every 4 hours dosing, levodopa Cmax declined by 44%.

The AUC and Cmax for carbidopa were 1.2-fold and 1.3-fold higher after administration of 25/100 mg dose every 4 hours compared to 12.5/50 mg dose administered every 2.0 hours. OCP noted that this decrease in exposure of CD after the half dosing is partly attributed to the food intake administration after 5 hours of the initial dose, because food intake decreased the exposure of CD. The PK profile of CD was "smoother" with the q2hr dosing regimen than expected, and there was no peak observed after the fourth dose of CD. This disappearance of the final peak was not well-understood, but OCP noted that dose proportionality of the lower dose was established using the in vitro dissolution profile, in which the split tablets (1/4th tablet, 6.25/25 mg CD/LD) and the whole tablet met the dissolution acceptance criteria.

OCP Recommendation: OCP recommends approval based on the bioequivalence demonstrated between Dhivy and the generic CD/LD 25/100 mg IR tablet.

5. Clinical/Statistical-Efficacy

The effectiveness of Dhivy is based on the demonstration of bioequivalence to the listed drug.

6. Safety

The safety of Dhivy is based on the demonstration of bioequivalence to the RLD. Dr. Leonard Kapcala, the clinical reviewer for this application, reviewed the new safety data in this submission. The safety review focused on the pivotal US bioequivalence study; however, Dr. Kapcala also reviewed safety data from the most recent PADER for the RLD.

There were no deaths or serious adverse events in Study 190051. There were three discontinuations in the study, all in patients who developed vomiting within 4 hours after dosing. The sponsor did not consider these withdrawals due to TEAEs but rather due to the risk of impacting the PK profile. The RLD is labeled for nausea and vomiting.

Clinical recommendation: Dr. Kapcala identified no new safety signal observed with this CD/LD 25/100 mg tablet. He recommends approval of this supplement and I agree with his recommendation.

7. Advisory Committee Meeting

None required, as this drug is not a new molecular entity.

8. Pediatrics

The submission did not include any pediatric data. Because Parkinson's disease generally does not occur in the pediatric population, a full waiver was granted for pediatric studies under Pediatric Research Equity Act (PREA).

9. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

The Division of Medication Error and Prevention Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP) provided consultations on the product labeling.

10. Recommendations/Risk-Benefit Assessment

The applicant has provided substantial evidence of the effectiveness and safety of Dhivy (immediate release carbidopa/levodopa 25 mg/100 mg tablets) based on bioequivalence to the listed drug.

No new safety signals were identified.

There are no outstanding unresolved issues.

Specific postmarketing risk management activities are not needed.

Agreement has been reached with the applicant on product labeling.

We agree with the review team that this NDA should be approved.

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/

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11/12/2021 10:44:11 AM

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