CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214869Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	214869
Supporting document/s:	0001
Applicant's letter date:	10/14/2020
CDER stamp date:	10/14/2020
Product:	(b) (4)/Dhivy®
Indication:	Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Applicant:	Riverside Pharmaceuticals Corporation
Review Division:	DN I
Reviewer:	LuAnn McKinney, DVM, DACVP
Supervisor:	Lois M. Freed, PhD
Division Director:	Eric Bastings, MD
Project Manager:	Stacy Metz, Pharm D

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214869 are owned by Riverside Pharmaceuticals Corp. or are data for which Riverside Pharmaceuticals Corp. has obtained a written right of reference. Any information or data necessary for approval of NDA 214869 that Riverside Pharmaceuticals Corp. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Riverside Pharmaceuticals Corp.does not own (or from FDA reviews or summaries of a previously approved application) are for descriptive purposes only and are not relied upon for approval of NDA 214869.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

This new drug application is for Dhivy, a (b) (4) tablet containing immediate release (IR) carbidopa (25 mg) and IR levodopa (100 mg) submitted under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The intended indication is Parkinson's disease patients (b) (4). The application relies on the Agency's previous findings of safety and effectiveness of Sinemet® CD/LD tablets at 25 mg/100 mg (NDA 17555 approved May 02, 1975).

Clinical development was conducted under IND 135441.

1.1.3 Labeling

There are no new findings regarding Levodopa or Carbidopa that would impact labeling.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were conducted in support of this marketing application.

1.3 Recommendation

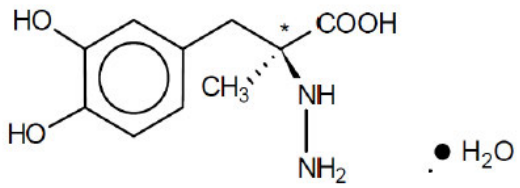
This New Drug Application is approvable from a nonclinical perspective.

2 Drug Information

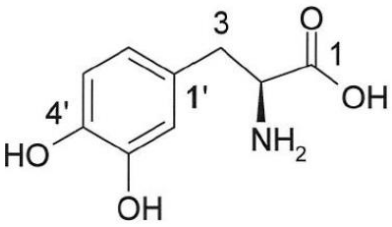
2.1 Drug

Generic Name: Carbidopa + Levodopa
Chemical Name:
CD- (S)-□-hydrazino-3,4-dihydroxy-□-methylbenzenepropionic acid
LD- monohydrate and (□)-(3,4-dihydroxyphenyl)-L-alanine
Molecular Formula/Molecular Weight:
CD- $C_{10}H_{14}N_2O_4.H_2O$ MW: 244.25
LD- $C_9H_{11}NO_4$ MW: 197.19
Structures: (from Sponsor)

CD



LD



Pharmacologic Class:

CD- aromatic amino acid decarboxlyase inhibitor
LD- aromatic amino acid

2.2 Relevant INDs, NDAs, and DMFs

IND 135441
Listed drug: NDA 017555, (Sinemet®) approved on May 02, 1975
DMF (b) (4)
DMF (b) (4)

2.3 Clinical Formulation

The drug product is a scored (b) (4) tablet containing immediate release (IR) carbidopa (25 mg) and IR levodopa (100 mg) that can be split into four segments containing equal amounts of carbidopa (6.25 mg) and levodopa (25 mg).

Sponsor's table:

(b) (4)

2.3.1 Comments on Excipients

There are no novel excipients. Tablets contain the inert ingredients microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

Sponsor's table:

Table 1. Excipients in (b) (4) Tablets

Material	(b) (4)
Pre-Gelatinized Starch (b) (4)	
Magnesium Stearate	
Microcrystalline Cellulose (b) (4)	

At the recommended maximum human dose of 8 tablets, the daily doses of magnesium stearate and pre-gelatinized starch (b) (4) are less than for approved drug products in the FDA Inactive Ingredient Database (IID). The sponsor noted that the total daily dose of (b) (4) mg of microcrystalline cellulose (MCC) exceeds the maximum daily exposure (MDE) of 2,828 mg for approved oral tablets and 3,195 mg for approved oral capsules. However, subsequent to NDA submission, in an updated record in the IID the MDE for a chronically administered oral solution is 5117 mg - which is greater than the daily dose of MCC at the MRHD.

Pharmaceutical grade MCC is commercially available as Avicel, Emcocel, Ceolus, Vivapur®, and Sanaq®. There are 33 entries for MCC in the IID: the maximum potency ranges from 1.6 (implant) to 837 mg (tablet, for suspension) per unit dose, and and MDE ranges from 132 (tablet) to 5117 mg (solution).

MCC has been extensively studied as a food substance. According to a 1993 CanTox© report submitted to the WHO, the daily US food intake of MCC was estimated to range from 5.1 to 10.2 g in young adult males. Although consumption of large quantities of celluloses may have a laxative effect, MCC is metabolically inert and not absorbed systemically following oral administration. In the agency's Food Additive Status list, MCC is a "substance permitted as an optional ingredient in a standardized food" and is an unlisted GRAS substance (has not been listed by the FDA in 21CFR).

In a 1998 report, the Microcrystalline Cellulose Committee (WHO Food Safety Additives Series 40) concluded that MCC had no effect on excretion, local (GI, lymphatic) particle dispersion, neonatal effects or on in vitro and in vivo genotoxicity assays. Due to the possible persorption of small particulates, the Committee retained the ADI "not specified" but revised the specifications for MCC to limit the content of particles less than (b) microns.

2.4 Proposed Clinical Population and Dosing Regimen

The intended clinical population is Parkinson's disease patients (b) (4) (b) (4) The proposed maximum recommended daily dose of Dhivy® is 8 tablets ((b) (4) mg CD/800 mg LD).

According to labeling for Sinemet®, the recommended initial daily oral dose in patients that are naïve to levodopa therapy is 25/100 mg TID for a daily total dose of 75/300 mg CD/LD and may be increased to a daily total of 200/800 mg CD/LD. If patients have been on therapeutic levels of levodopa, daily doses may be increased to 100/1000 mg CD/LD.

2.5 Regulatory Background

IND 135441 was submitted on 06/07/2019
NDA 214869 was submitted on 10/14/2020

3 Studies Submitted

3.1

No nonclinical studies were submitted.

3.2 Previous Reviews Referenced

Nonclinical review of IND 135441, LuAnn McKinney, DVM, DACVP. July 26, 2019.

4. Integrated Summary and Safety Evaluation

This new drug application for Dhivy, is a 505 (b)(2) application and relies on the Agency's previous findings of safety and efficacy of the Sinemet® (NDA 17555 approved May 22, 1975). The intended indication is for Parkinson's disease patients (b) (4) Dhivy® has been established as clinically bioequivalent to the listed drug and, therefore, no nonclinical testing is necessary.

At the maximum recommended human dose, all excipients are within acceptable limits, based on the FDA's Inactive Ingredient Database.

Conclusion

From a nonclinical perspective, this marketing application is approvable.

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/

LUANN MCKINNEY
11/08/2021 11:25:37 AM

LOIS M FREED
11/08/2021 01:16:58 PM
I concur.