CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209184Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209184
Review 1

Drug Name/Dosage Form	Inbrija™ (levodopa) inhalation powder
Strength	42 mg
Route of Administration	Oral inhalation
Rx/OTC Dispensed	Rx
Applicant	Acorda Therapeutics
US agent, if applicable	N/A

Quality Review Team

Discipline	Primary Reviewer	Secondary Reviewer
Drug Substance	Charles Jewell	Ali al-Hakim
Product and Labeling	Dan Berger	Wendy Wilson-Lee
Process	Yaodong (Tony) Huang	Nallaperumal Chidambaram
Microbiology	N/A	--
Facility	Steve Hertz	Ruth Moore
Biopharmaceutics	Akm Khairuzzaman	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

CDRH Review Team

Discipline	Reviewer	Organization
Lead Reviewer	Brandon Blakely	CDRH/ODE/DAGRID/RPDB
Device Biocompatibility	BiFeng Qian	CDRH/ODE/DAGRID/INCB
Cleaning/Disinfection	Christopher Dugard	CDRH/ODE/DAGRID/INCB

Submissions Reviewed	Document Date	Disciplines Affected
SD-01, Original submission	12/16/2015	All
SD-09, Resubmission after Refuse to File	03/28/2017	All
SD-10, Response to IR	03/01/2018	Product, CDRH
SD-13, Response to IR	04/05/2018	Product
SD-15, Response to IR	04/30/2018	Biopharmaceutics
SD-16, Labeling/Container	05/25/2018	Labeling
SD-18, Response to IR	06/29/2018	Product
SD-19, Response to IR	07/05/2018	CDRH
SD-20, Labeling/Container	07/09/2018	Labeling
SD-21, Response to IR	08/03/2018	Process
SD-24, Response to IR	08/21/2018	Process
SD-26, Response to IR	09/05/2018	CDRH
SD-27, Response to IR	09/09/2018	CDRH
SD-28, Response to IR	09/10/2018	CDRH
SD-28, Response to IR	09/14/2018	CDRH

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)		Adequate	07/30/2018	C. Jewell
	II			Adequate	06/08/2018	D. Berger
	III			N/A [2]	--	
	III			N/A [2]	--	
	III			N/A [2]	--	
	III			N/A [2]	--	
	IV			N/A [2]	--	
	IV			N/A [2]	--	

(b) (4)

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

Document	Application Number	Description
IND	115750	Sponsor: Acorda Development of levodopa inhalation powder
NDA	17555	Sponsor: Merck & Co. SINEMET® (carbidopa and levodopa) tablets Referenced under 505(b)(2) to support safety and efficacy of levodopa.

2. CONSULTS

Device aspects were consulted to CDRH. The CDRH review team recommends approval of the NDA.

Executive Summary

I. Recommendations and Conclusion on Approvability

The OPQ review team recommends **Approval** of NDA 209184, Inbrija™ (levodopa) inhalation powder. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) Including Intended Patient Population	Treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen
Duration of Treatment	Chronic
Maximum Daily Dose	420 mg
Alternative Methods of Administration	None

Levodopa is an endogenous aromatic acid biosynthesized from L-tyrosine. Levodopa readily crosses the blood-brain into the central nervous system, where is it is converted by the enzyme aromatic L-amino acid decarboxylase (AADC) to the neurotransmitter dopamine. Levodopa was approved in 1970 (as Larodopa capsules, Hoffman LaRoche), for treatment of Parkinson's disease. Subsequently, fixed dose combination products (e.g., Sinemet, marketed by Merck) that contain levodopa and a peripheral AADC inhibitor, carbidopa, were developed. Currently, no products containing levodopa as a single entity are marketed in the U.S.

Acorda Therapeutics (Acorda) seeks approval of a drug/device combination product for administration of levodopa as an inhalation powder. The product is intended to treat episodes of hypomobility (OFF periods) associated with pharmacokinetic (PK) variability following oral administration of carbidopa and levodopa (CD/LD). Acorda indicates that pulmonary delivery of levodopa could provide more rapid delivery of levodopa (versus oral delivery) and, thus, rapid relief of hypomobility.

B. Quality Assessment Overview

The proposed drug/device combination product comprises hypromellose (HPMC) capsules containing a spray-dried formulation of levodopa (42 mg), 1,2-dipalmitoyl-*SN*-glycero-3-phosphocholine (DPPC), and sodium chloride, to be administered using a co-packaged proprietary breath-actuated inhaler [Figures 1 – 3 below].

Source: Module 3.2.R.1 Device Composition

The proposed commercial configuration is a carton containing 92 blister packaged capsules and one inhaler. To administer a dose (84 mg, 2 capsules), the patient removes the outer cap and mouthpiece, then places one capsule in body of the device. When the mouthpiece is reattached, the device punctures the capsule and is ready for use. The patient is instructed to: 1) breathe out; 2) place the mouthpiece into their mouth; 3) breathe in deeply until the they hear and feel the capsule spinning; 4) take the inhaler out of their mouth; 5) hold their breath for 5 seconds and then exhale. The first capsule is removed from the device and a second capsule is administered in the same manner. The inhaler should be discarded after all capsules have been administered.

The OPQ review team focused on evaluation of submitted manufacturing and control information to support the quality of the drug component and its compatibility with the device, and on the adequacy of the controls for the finished combination product to ensure the safety and efficacy of the dose delivered to the patient. The Center for Devices and Radiological Health (CDRH) evaluated the design, safety/biocompatibility, and performance of the device component.

Drug Substance

Levodopa is a well-characterized small molecule that is approved under multiple NDAs and ANDAs. Information regarding manufacture and control of the bulk drug substance is incorporated by cross-reference to DMF (b) (4) The information submitted directly to the NDA regarding general properties of levodopa, potential impurities, specifications, and analytical procedures, is consistent with the manufacturer's DMF and USP monograph requirements.

Combination Product

Drug Component

The drug component of the combination product is a spray-dried formulation 42 mg levodopa, USP; 3.7 mg 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC); and (b) (4) Sodium Chloride, USP in a white, size 00 Hypromellose (HPMC) capsule. The recommended dose, 84 mg, requires administration of two capsules.

Formulation development for Inbrija focused on identification of: a) inhalable excipients compatible with levodopa; and b) drug and excipient ratios that would produce a powder with a (b) (4) and suitable aerosol properties. The resulting powder formulation containing levodopa, DPPC and sodium chloride in a (b) (4) weight-based ratio was used in all clinical trials; (b) (4)

(b) (4)

(b) (4) The capsules are then co-packaged with the inhaler in a carton containing 92 packaged capsules and one inhaler.

Device Component

The inhaler is a simple metered dose inhaler. Device performance (reviewed by OPQ) and supporting data for device robustness (reviewed by CDRH) were deemed adequate. The CDRH team identified deficiencies related to biocompatibility of direct and indirect patient contact surfaces. These deficiencies, which were related to inadequate testing for extractables/leachables, volatile organic compounds, and fine particles were resolved based on data from additional testing performed by the applicant during the review cycle.

Product Specification

The specification for the finished combination product includes appropriate tests for the drug component (appearance, assay, impurities, content uniformity of the filled capsules, powder morphology/XRPD, (b) (4) and microbial enumeration) and performance of the assembled product (emitted dose, dose uniformity, aerodynamic

particle size distribution and microscopic evaluation, and foreign particles). All analytical procedures are adequately described and validated.

Expiration Dating

The stability data provided support a shelf-life of 24 months, calculated from date of capsule manufacture, for levodopa capsules, and up to 24 months, calculated from date of capsule manufacture, for the finished product, when stored at USP controlled room temperature. It is noted that a longer shelf life (39 months) may be assigned to the inhaler. However, the shelf life for the product is limited by the component with the shortest expiry.

Facilities

All facilities that will be involved in commercial manufacture and testing of levodopa and levodopa powder for inhalation (capsules), and the inhaler are currently acceptable.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31 (b). Assuming all U.S. patients use the product and no metabolism occurs, the expected introduction concentration (EIC aquatic), would be significantly below 1 ppb. The applicant states that, to their knowledge, no extraordinary circumstances exist. Thus, the claim for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment for Inbrija (levodopa) Inhalation Powder

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 (capsule)	Formulation, raw materials, moisture, air, container closure, process parameters, scale, equipment (excipient reactions, oxidation, hydrolysis)	**L**	(b) (4)	**Adequate**	
Content uniformity (capsule)	Formulation, raw materials, process parameters, scale, equipment *(spray dried powder not uniform, poor flow properties, segregation)*	**L**		**Adequate**	
Physical stability, solid state (capsule)	Formulation, process parameters, (b) (4), container closure.	Not included in initial risk assessment		**Adequate**	
Microbial limits	Formulation, raw materials, process parameters, moisture, container closure (packaging defects)	**L**		**Adequate**	
Emitted dose	Capsule content, (b) (4) *(capsule fill adhering to shell)*, device design	Not included in initial risk assessment		**Adequate**	
Delivered dose uniformity (DDU)	Capsule CU, container, device design, particle size distribution (b) (4) (b) (4) *aggregation, airflow resistance deviation, device malfunction*)	**M**		**Adequate**	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Aerodynamic particle size distribution (APSD)	Capsule CU and particle size distribution, container, device design (b) (4) *inhalable fraction too low or too high)*	**M**	(b) (4)	**Adequate**	
Foreign matter	Particulates from excipient, solvents, equipment, HPMC capsules, device components	**L**		**Adequate**	

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Adequate
Dosage form, route of administration	Adequate
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Adequate

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Adequate

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Adequate
Strengths: in metric system	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Adequate

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Adequate
Dosage form and route of administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	NA
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Adequate, based on chemical class description
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Adequate

5. *Section 16 How Supplied/Storage and Handling*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate
Available units (e.g., bottles of 100 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	Adequate
Storage conditions	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

Reviewer's Assessment of Package Insert: ***Adequate***
The Prescribing Information meets all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Adequate	Adequate
Dosage strength	Adequate	Adequate
Net contents	Adequate	Adequate
"Rx only" displayed prominently on the main panel	Adequate	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Adequate	Adequate
Lot number and expiration date (21 CFR 201.17)	Adequate	Adequate
Storage conditions	NA for small blister labels	Adequate
Bar code (21CFR 201.25)	Adequate	Adequate
Name of manufacturer/distributor	Adequate	Adequate
And others, if space is available		

Reviewer's Assessment of Labels: ***Adequate***
The labels comply with all regulatory requirements from a CMC perspective.

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate

No deficiencies have been identified. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Reviewer Name and Date:

Dan Berger July 24, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Wendy Wilson July 24, 2018

Dan Berger

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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
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BIOPHARMACEUTICS

NDA: 209184 (Sequence 0008); 505(b)(2)
Drug Product Name/Strength: INBRIJA™ (levodopa inhalation powder), for oral inhalation use/ 42 mg
Route of Administration: Oral inhalation
Applicant Name: Acorda Therapeutics, Inc.
Submission Date: December 5, 2017 (Re-submission)

Background: Acorda Therapeutics is seeking approval for Inbrija® (levodopa inhalation powder) under the 505(b)(2) path, relying upon FDA's previous findings of safety and efficacy for the approved Sinemet® oral tablets (NDA 017555) as the listed drug. The drug product is to be administered by oral inhalation for the treatment of symptoms of OFF periods in Parkinson's disease (PD) as an adjunct to a carbidopa (CD)/levodopa (LD) regimen. The proposed drug product is a dry powder levodopa formulation supplied in 42 mg strength capsule that are designed for oral inhalation using the proprietary CVT-301 dry powder inhaler. It is a drug-device combination drug product with a new dosage form, new formulation, and new route of administration for this drug. The proposed dose in adult PD patients is 84 mg administered as two 42 mg capsules for inhalation up to 5 times per day.

The clinical package in support of this NDA includes the results of 6 Phase I studies (safety, tolerability, and pharmacokinetics), 2 Phase II studies (safety, PK and efficacy), and 3 Phase III (safety and efficacy) studies in patients with Parkinson's disease. A Phase 1 bioavailability bridging Study CVT-301-010 was conducted to compare the proposed commercial CVT-301 product to listed drug Sinemet®.

REVIEW SUMMARY

The Biopharmaceutics review focused on the evaluation of the adequacy of relevant information/data, as summarized below:

1) ***Dissolution Method and Acceptance Criteria:*** It was found to be not relevant for this product, since it is an oral dry powder inhalation product. According to the Applicant, the proposed dry powder dosage form allows for rapid powder dissolution and uptake of LD from the CVT-301 drug product.

2) ***Bridging of Formulations:*** The formulation of the drug product (b) (4) LD:DPPC:NaCl composition) used in the pivotal clinical studies is the same as that of the proposed commercial CVT-301 drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, no further bridging between the clinical and commercial formulation products is needed. Refer to Office of Clinical Pharmacology (OCP) review for results of in-vivo bridging between the proposed commercial product and the listed drug Sinemet®.

3) ***Biowaiver Request:*** No biowaiver request was submitted in the submission since only one 42-mg strength will be marketed.

4) ***BCS Classification:*** The BCS class of LD has not been designed by the FDA. The Applicant reported that, citing literature data source, oral LD belongs to BCS Class-1, being high solubility and high permeability [minimum dose: 100 mg (oral tablet); maximum dose: 250 mg (oral tablet)].

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 209184 for INBRIJA™ (levodopa inhalation powder), 42 mg, for oral inhalation use is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Akm Khairuzzaman, PhD **8/31/2018**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Ta-Chen Wu, PhD **8/31/2018**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Akm Khairuzzaman

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Ta-Chen Wu

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Martha Heimann

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Comments: This is a corrected version of the combined assessment document uploaded on 11/30/2018. The wrong labeling review (unrelated NDA) was included in the previous file.