

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203952Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

TO: OFFICE OF NEUROLOGY PRODUCTS
FROM: CHARLES JEWELL, CMC REVIEWER, BRANCH 1, DIVISION 1, ONDQA
SUBJECT: REVIEW OF NDA 203952 (DUOPA; ABBVIE; (CARBIDOPA AND LEVODOPA) ENTERAL SUSPENSION; CMC FINAL APPROVAL RECOMMENDATION
DATE: DECEMBER 9, 2014
CC: TRACY PETERS, RPM
 DAVE PODSKALNY, CDTL

In the previous CMC review submitted on 10 November 2014, the quality recommendation was for approval, pending the final approval recommendation from ONDQA Biopharmaceutics, CDRH Devices and the overall site recommendation from the Office of Compliance. Since then, approval recommendations have been provided by these three quality disciplines to support the APPROVAL recommendation by CMC.

The following should be communicated to the sponsor in the approval letter:

The Agency is assigning an expiration dating period for DUOPA of 24 months when stored frozen (-20°C) and 12 weeks stored at refrigerator temperature (2 to 8°C). Once the product has thawed to room temperature, it is to be used the same day or discarded.

- The ONDQA Biopharmaceutics review submitted by Kelly Kitchens on 02 December 2014 provided an approval recommendation. The following is copied from the review that is filed in Panorama:

RECOMMENDATION:

The Applicant provided adequate data to support the proposed dissolution acceptance criterion of Q = (b) (4) at 40 minutes for carbidopa and levodopa. The following method and acceptance criterion are acceptable for release and stability testing.

USP Apparatus	Rotation Speed	Medium/Temp	Volume	Carbidopa and Levodopa Acceptance Criterion
2 (Paddle)	25 rpm	0.05 M acetate buffer, pH 4.5 at 37°C	500 mL	Q = (b) (4) at 40 minutes

From the Biopharmaceutics perspective, NDA 203952 for Duopa (carbidopa and levodopa enteral suspension) is recommended for APPROVAL.

Signature

Kelly M. Kitchens -S
 Digitally signed by Kelly M. Kitchens -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000336574, cn=Kelly M. Kitchens -S
 Date: 2014.12.02 09:21:08 -05'00'

Kelly M. Kitchens, Ph.D.
 Biopharmaceutics Reviewer
 Office of New Drug Quality Assessment

Signature

Okponanabof a Eradiri, Ph.D.
 Digitally signed by Okponanabofa Eradiri, Ph.D.
 DN: cn=Okponanabofa Eradiri, Ph.D., o=ONDQA, ou=Biopharmaceutics, email=okpo.eradiri@fda.hhs.gov, c=US
 Date: 2014.12.02 10:04:35 -05'00'

Okpo Eradiri, Ph.D.
 Acting Biopharmaceutics Team Leader
 Office of New Drug Quality Assessment

cc. ADorantes; PSeo

CMC REVIEW OF NDA 203312 AFTER COMPLETE RESPONSE

- The CDRH Devices reviewer (Alan Stevens) submitted a consult review to the OND RPM (Tracy Peters) and CDTL (Dave Podskalny) on 03 December 2014 recommending approval. The following is copied from the CDRH consult review:



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: December 3, 2014

From: CDR Alan Stevens, Reliability and Mechanical Engineering
OMPT/CDRH/ODE/DAGRID/GHDB

To: Dr. Tracy Peters, Senior Regulatory Health Project Manager
OMPT/CDER/OND/ODEI/DNP

and

Dr. Gerald Podskalny, Clinical Team Leader
OMPT/CDER/OND/ODEI/DNP

Subject: CDRH Consult for NDA 203952, infusion pump for enteral delivery of Levodopa / Carbidopa
Intestinal Gel

Drug Applicant: AbbVie
Device Sponsor: Smiths Medical
Device Name: CADD Legacy 1400 Pump System

Recommendation: Approve

V. Decision Recommendation

All CR deficiencies related to the infusion device have been adequately addressed. I recommend approval.

Digital Signature Concurrence Table	
Reviewer	<p>Alan M. Stevens -S</p> <p>Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2014.12.03 16:10:32 -05'00'</p>
Team Leader	<p>Ryan J. Mcgowan -S</p> <p>Digitally signed by Ryan J. Mcgowan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000352462, cn=Ryan J. Mcgowan -S Date: 2014.12.03 16:50:03 -05'00'</p>
Supervisor	<p>Richard C. Chapman -A</p> <p>Digitally signed by Richard C. Chapman -A Date: 2014.12.03 17:07:03 -05'00'</p>

- The Office of Compliance granted an overall acceptable recommendation for this application on 28 March 2014. Two of the sites were due for re-evaluation in December of 2014. At the request of the CMC reviewer, Office of Compliance reviewer Juandria Williams conferred with the districts for the sites due to require re-evaluation in December 2014 and the re-evaluation date was extended to 31 March 2015 based on district recommendation. This was reported in Panorama as a comment by Juandria on 13 November 2014.

CMC REVIEW OF NDA 203312 AFTER COMPLETE RESPONSE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application:	NDA 203952/000	Action Goal:	
Stamp Date:	16-NOV-2012	District Goal:	27-JAN-2014
Regulatory:	11-JAN-2015		
Applicant:	ABBVIE 1 NORTH WAUKEGAN RD DEPT PA77 BLDG AF NORTH CHICAGO, IL 60064	Brand Name:	CARBIDOPA AND LEVODOPA ENTERAL SUSPENSIO
		Estab. Name:	
		Generic Name:	CARBIDOPA AND LEVODOPA ENTERAL SUSPENSIO
Priority:	3	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	120		001; GEL; CARBIDOPA; 5MG 001; GEL; LEVODOPA; 20MG

Application Comment:

FDA Contacts:	C. JEWELL	Prod Qual Reviewer		3017964232
	T. BOUIE	Product Quality PM		3017961649
	S. METZ	Regulatory Project Mgr	(HFD-120)	3017962139
	M. HEIMANN	Team Leader		3017961678

Overall Recommendation:	ACCEPTABLE	on 28-MAR-2014	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 28-MAR-2014	by EES_PROD		
	ACCEPTABLE	on 07-MAR-2014	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 27-AUG-2013	by EES_PROD		
	PENDING	on 20-AUG-2013	by EES_PROD		
	PENDING	on 19-JUN-2013	by EES_PROD		
	PENDING	on 03-DEC-2012	by EES_PROD		



**Charles
Jewell -S** Digitally signed by Charles
Jewell -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Charles Jewell -S,
0.9.2342.19200300.100.1.1=2000
403529
Date: 2014.12.10 16:49:34 -05'00'

**Olen
Stephens -S** Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2014.12.10 13:29:14 -05'00'



NDA 203952

Office of Neurology Drug Products

CMC Review # 3 by Charles Jewell

Review Date: 11/10/2014

Drug Name/Dosage Form	Duopa (Carbidopa and Levodopa) enteral suspension
Strength/Potency	Carbidopa is 4.63 mg/mL and Levodopa is 20 mg/mL
Route of Administration	Continuous infusion by pump through NJ-Tube or PEG-Tube each with jejunal extension
Rx/OTC Dispensed	Rx
Applicant/Sponsor	Abbvie
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
eCTD 0033 - /Resubmission/ Class 2	07/11/2014
eCTD 0034 - Quality/Response to IR	08/22/2014
eCTD 0036 - Quality/Stability Information	09/11/2014
eCTD 0037 - Multiple Categories	10/31/2014

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Charles Jewell	
Drug Product	Charles Jewell	
Process	NA	
Microbiology	NA	
Facility		Office of Compliance
Biopharmaceutics	Kelly Kitchens	
Project/Business Process Manager	Teshara Bouie	
Application Technical Lead	NA	
Laboratory (OTR)	NA	
ORA Lead	NA	
Environmental Assessment (EA)	NA	

Table of Contents

Quality Review Data Sheet 4

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2)..... 4

2. RELATED/SUPPORTING DOCUMENTS: 4

3. CONSULTS:..... 4

Executive Summary	5
I. Recommendations	5
A. Recommendation and Conclusion on Approvability	5
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	6
II. Summary of Quality Assessments	6
• Drug Substance [USAN Name] Quality Summary	6
• Drug Product [Established Name] Quality Summary	7
• Summary of Drug Product Intended Use	9
• Biopharmaceutics Considerations	10
• Novel Approaches/Precedents	11
• Any Special Product Quality Labeling Recommendations	11
• Facility Information	11
III. Lifecycle Knowledge Management	11
Review Section	13
Background for Resubmission after Complete Response from the Drug Substance/Drug Product Quality Perspective	13
Summary of Applicant's Response to Deficiency #1:	14
Summary of the Applicant's Response to Deficiency #2:	14
Summary of Applicant's Response to Deficiency #3:	14
Summary of the Applicant's Response to Deficiency #4:	15
Summary of the Applicant's Response to Deficiency #5:	15
Additional Comments (Product Quality)	15
Summary of the Applicant's Response to Additional Comment #1:	15
Summary of the Applicant's Response to Additional Comment #2:	15
Product Quality Information Requests After the Resubmission	16
Product Quality Information Request sent October 9, 2014 (Mid-Cycle by Tracy Peters)	16
Product Quality Information Request sent October 20, 2014 (by Tracy Peters)	18
Amendment eCTD 0036 (9/11/2014) Provision of Full 15 Weeks Stability Data at Refrigerated Storage Conditions	19
eCTD Sections	20
3.2.P.5.1 Specification for Levodopa - Carbidopa Enteral Suspension	20

3.2.P.8.1 Stability Summary and Conclusions for Levodopa-Carbidopa Enteral Suspension	23
3.2.P.8.2 Post Approval Stability Protocols.....	25
3.2.P.8.3 Stability Data	27

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	N/A	see review #1 for this NDA	LOA 4/19/2013
	Type II			N/A	see review #1 for this NDA	LOA 4/19/2014
				N/A	see review #1 for this NDA	LOA 4/17/2013
	Device Master File			Under review by CDRH	pending	LOA 4/17/2014

Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60663	IND for this product

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharm/Tox				
CDRH:Pump Review	under review	pending		Alan Stevens
CDRH: Human Factors	complete	acceptable response to CR issues	10/17/2014	QuynhNhu Nguyen

Clinical				
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend approval based on CMC, pending approval recommendation from Biopharmaceutics, the overall site recommendation from the Office of Compliance and the recommendation from CDRH on the device portions of this product.

a. Summary of Complete Response issues

1. The applicant adequately addressed the issue of describing the (b) (4) identified in the previous review cycle. The applicant adequately described when the two different methods (b) (4) will be used.
2. The applicant provided the required refrigerated stability data, 8 weeks of data at resubmission, and updated data sets through the final to 15 weeks in an amendment. The stability data includes a morning dose measurement to demonstrate homogeneity. In addition the applicant proposed a potentially better measure of homogeneity known as the Uniformity of Dispensed Cassette Contents. This method was adequately described in the resubmission, and testing by this method was included in the release specification for refrigerated stability. Also, a plan was initiated to further develop this version of Content Uniformity Testing.
3. The required dissolution data was provided, and adequacy is being evaluated by the biopharmaceutics reviewer.
4. All required data was provided and found to be adequate. The dissolution data is covered in biopharmaceutics review.
5. The sponsor confirmed the correct value for the slope of decrease of (b) (4) was (b) (4) mg/mL/week (not (b) (4) mg/mL per week).

b. Action letter language, related to critical issues such as expiration date

If the application is approved, the expiration dating period for this drug product is no more than 24 months when stored frozen (-20°C) and no more than 12 weeks when stored at refrigerated temperature (2°C to 8°C). When warmed to room temperature it should be used the same day or discarded.

c. Benefit/Risk Considerations

This drug product, including its associated administration system, is complicated to use, and the drug product has critical storage requirements to curtail degradation and loss of suspension homogeneity. Hydrazine is a known degradant that is potentially genotoxic, and can be present up to (b) (4) pm (based on suspension weight) in the product. Exposure from one medication cassette per day could expose a patient to up to (b) (4) mg of hydrazine per day. The consequences of exposure to this level of hydrazine is not completely known. However, this drug product may provide unprecedented control of levodopa levels which is not achieved by oral administration of levodopa. This has the potential to dramatically improve quality of life to the advanced Parkinson's patient, where oral levodopa is not adequately effective in reducing off-time for patients. For the patient population that this drug product is intended, the risk of hydrazine exposure, other degradants and surgical intervention to place the PEG-J tubing may be worthwhile in order to obtain a significant benefit in quality of life (reduced off-time).

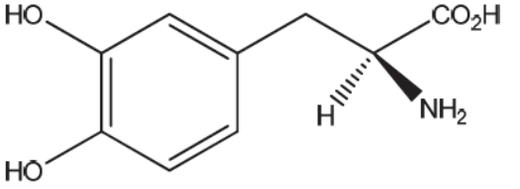
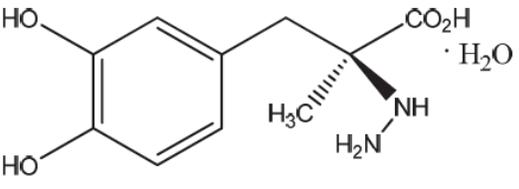
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant commits to placing the first ten commercial batches on stability. All ten lots will be tested by the Uniformity of Dispensed Cassette Content (UDCC) (for carbidopa and levodopa) using three cassettes (immediately proceeding to Level 2 UDCC testing by testing n = 3 cassettes [10 fractions per cassette = 30 fractions]). This is proposed to verify the value of the UDCC method as a control of homogeneity. After the first ten batches, annual testing of UDCC will be done using only 1 cassette per the annual stability commitment. The applicant has agreed (b) (4) it will require a prior-approval supplement.

II. Summary of Quality Assessments

• **Drug Substance [USAN Name] Quality Summary**

a. Chemical Name or IUPAC Name/Structure

	
<p style="text-align: center;">Levodopa</p> <p>(S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid $C_9H_{11}NO_4$ MW: 197.19</p>	<p style="text-align: center;">Carbidopa Monohydrate</p> <p>(S)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid $C_{10}H_{14}N_2O_4 \cdot H_2O$ MW: 244.24 (as monhydrate)</p>

b. Properties/CQAs Relevant to Drug Product Quality

- Carbidopa is slightly soluble in water, freely soluble in dilute hydrochloric acid. As the monohydrate it is a white to creamy white powder. It melts between 203°C and 205°C. It has a single chiral center. (b) (4)
- Levodopa is slightly soluble in water, freely soluble in dilute hydrochloric acid. It is a white to off-white crystalline powder. It melts between 276 and 278°C. It has a single chiral center. (b) (4)

- c. List of starting materials
- d. Suppliers of starting materials (site)
- e. Summary of Synthesis
- f. Process
 - i. (b) (4) as applicable
 - ii. Critical equipment

- Carbidopa is manufactured and (b) (4) at (b) (4) under DMF # (b) (4). Starting materials and manufacturing process conditions are adequately described therein.
- Levodopa is manufactured and (b) (4) at (b) (4) under DMF# (b) (4). Starting materials and manufacturing process conditions are adequately described therein.

g. Container Closure

- Carbidopa is packaged (b) (4)
- Levodopa is packaged (b) (4)

h. Retest Period & Storage Conditions

- Carbidopa has a retest period of (b) (4) months supported by long term storage data obtained at 30°C/65% RH and accelerated stability studies.
- Levodopa has a retest period of (b) (4) months supported by long term storage data obtained at 30°C/65% RH and accelerated stability studies.

- **Drug Product [Established Name] Quality Summary**

a. Strength

This drug product is manufactured in one strength. It is an enteral suspension with a content of carbidopa at 4.63 mg per mL and a content of levodopa at 20.0 mg per mL. Carbidopa is expressed in terms of anhydrous carbidopa which is equivalent to 5.0 mg per mL of carbidopa monohydrate.

b. Description/Commercial Image

100 grams of enteral suspension (approximately 100 mL) is filled into a plastic bag which is contained in a plastic medication cassette (reservoir) designed for use specifically with the infusion pump manufactured by Smiths Medical known as the CADD-Legacy Pump Model 1400 described in MAF# (b) (4)

c. Summary of Product Design

The drug product is designed as a stable suspension which gets pumped continuously into a percutaneous endoscopic gastrostomy tube with a jejunal extension tube (PEG-J). This allows release of the suspension directly into the jejunum. The product needs to remain as a stable suspension but have a low enough viscosity that is can still be readily pumped. The suspension needs to be adequately stable at near body temperature for at least 16 hours.

d. List of Excipients:

- Carmellose sodium, USP (b) (4) mg per mL)
- Purified water, USP

e. Process Selection (Unit Ops Summary)



f. Container Closure

It is a 100 mL Medication Dosing Cassette manufactured by (b) (4)

g. Expiration Date & Storage Conditions

The drug product is stable for up to 24 months when stored frozen (-20°C). It is stable for 12 weeks when stored at refrigerator temperature (2 to 8°C). By design, it will be shipped from the manufacturer frozen to the pharmacy where it should be stored frozen. Prior to dispensing, the pharmacy should allow it to thaw in the refrigerator (b) (4). The patient should store it in the refrigerator and use prior to 12 weeks after start of thawing in the pharmacy. It must be used the same day when allowed to thaw to room temperature. The pharmacist should label the cartons with the appropriate use-by date.

h. List of co-packaged components

The drug product is packaged in cartons of seven medication dosing cassettes. The drug product is designed for use with the CADD Legacy Pump Model 1400 which is distributed separately with appropriate connection tubing. The PEG-J tubing set and Naso-Jejunal (NJ) sets are sold separately and must be installed by appropriate medical personnel. The PEG-J tube installation requires surgery. The proper placement of the Jejunal tubing requires endoscopic guidance.

- **Summary of Drug Product Intended Use**

One medication cassette contains a total of 2000 mg of levodopa, 500 mg of carbidopa monohydrate and (b) (4) mg of carmellose sodium. The cassette is designed for use in an administration system which involves an infusion pump that connects to either naso-jejunal (NJ) tubing or percutaneous endoscopic gastrostomy (PEG) tubing which is connected to jejunal (J) tubing. The pump is designed to work with the cassette to deliver a continuous infusion of the enteral suspension directly to the jejunum.

The pump is programmed to deliver a morning dose (bolus rate higher than the normal infusion rate), the continuous infusion and extra doses (short bursts at a higher than normal infusion rate). The pump has three lock levels for programming. Level 0 and level 1 require passcodes and are designed for original set-up by the physician and for the main health care provider. Level 2 is set for use by the patient, with limited controls. Level 2 allows only stopping and starting the pump, reset of the reservoir volume, starting an extra dose and starting the morning dose. Level 2 does not allow any programming. The morning dose and extra dose mode accelerates the pumping over the continuous rate during the bolus periods. There is one morning dose and a number of extra doses may be allowed, as determined by the physician level programmer. The maximum possible continuous rate is 20 mL/hr. This rate can be varied in level 1. Maximum accessible rate can be programmed in level 0. Continuous dosing can vary from 0.0 mL/hr. to 20.0 mL/hr. in 0.1 mL/hr. increments. The morning dose can be set in 0.1 mL increments to a maximum of 20 mL. The extra dose can be set in 0.1 mL increments to a maximum of 9.9 mL. The rate for an extra dose or morning dose can be

as high as 40 mL/hr., the continuous rate plus the fastest rate to achieve the bolus dose. The pump can operate at 125 mL/hr. in priming mode.

The control for number of morning doses or extra doses is achieved by locking out a new dose for a set period of time. The morning dose lockout is from 1 to 24 hours in 1 hour increments. The extra dose lockout is from 15 minutes to 24 hours in 15 minute increments.

The maximum normal dose is intended to be one medication cassette per day. A day is intended to cover a 16 hour continuous infusion period. It is not intended to be used while the patient is sleeping. It should be noted that in efficacy studies, a significant number of patients received more than one cassette per day.

Proprietary Name of the Drug Product	DUOPA
Non Proprietary Name of the Drug Product	Carbidopa and Levodopa Enteral Suspension
Non Proprietary Name of the Drug Substance	Carbidopa, Levodopa
Proposed Indication(s)	Long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)
Duration of Treatment	16 hours daily; chronic
Maximum Daily Dose	2000 mg levodopa (intended)
Intended Patient Population(s)	Orphan Drug Population: as indicated in proposed indication.
Alternative Methods of Administration	administered through PEG-J tube or NJ tube set directly to Jejunum. No other alternatives.

- **Biopharmaceutics Considerations**

Reviewer Comment: See the biopharmaceutics review for this information.

- BCS Classification:
 - Drug Substance:
 - Drug Product:
- Biowaivers/Biostudies
 - Biowaiver Requests
 - PK studies
 - IVIVC
- Summary of Regulatory Dissolution Method & Acceptance Criteria

PARAMETER	VALUE
Apparatus	

PARAMETER	VALUE
Medium	
Volume	
Temperature	
Rotational Speed	
Analytical Method	
Specification	

- **Novel Approaches/Precedents**

This is the first enteral suspension designed to be delivered directly to the jejunum, and the idea of continuous delivery is relatively novel. The development of the Uniformity of Dispensed Cassette Contents (UDCC) measure, based on USP Content Uniformity may be a precedent setting assay for this type of suspension product.

- **Any Special Product Quality Labeling Recommendations**

(b) (4)
 Due to the precedence of other carbidopa and levodopa containing drug product we are requiring the content of carbidopa to be based on anhydrous carbidopa which is 4.63 mg per mL. The European version of this product is marketed as 5.0 mg per mL based on carbidopa monohydrate.

- **Facility Information**

The recommendation from the Office of Compliance is pending.

III. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking	Justification	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations / Comments**

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking	Justification	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations / Comments**
Particle Size Distribution for Carbidopa and Levodopa	M	(b) (4)	(b) (4)	Acceptable	Particle size distribution outside the specified range has not been adequately studied

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Risk Ranking *	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments**
Homogeneity of the drug product	(b) (4)	H	(b) (4) Now the applicant is using Uniformity of Dispensed Cassette Contents as a better measure of content uniformity throughout the full contents of the cassette.	Acceptable	Homogeneity is the most critical quality attribute for this product. Homogeneity is conserved for at least 24 months for frozen product. The refrigerated product is demonstrated homogeneous for 12 week (b) (4) Product is not stable at ambient temperature for more than a day.

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Risk Ranking *	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments**
Degradation Impurity Levels	(b) (4)	H	Product should be maintained frozen until dispensed by a pharmacist trained in the knowledge of this drug product. Once dispensed, should be stored refrigerated and used within 12 weeks. Once brought to room temperature should be used the same day or discarded	Acceptable	We are allowing up to (b) (4) ppm of hydrazine in this drug product (based on weight of the suspension) Up to (b) (4) ng per casse exposure. Long term risk is unknown. Any increase in in-use period of refrigerated or room temperature stored product should be supported by hydrazine exposure data/justifications

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

Review Section

Background for Resubmission after Complete Response from the Drug Substance/Drug Product Quality Perspective

The previous submission of this application was given a complete response. There were five product quality related deficiencies cited.

1. The analytical method for determining the (b) (4) should be adequately described and validated and included in the drug product specification for release and stability, with appropriate limits. It is not adequate to use this only as an in-process method control listed in the Master Batch Record. Also, clarify which method (b) (4) will be used and the conditions under which the two methods would be used.

Summary of Applicant's Response to Deficiency #1:

-
-

(b) (4)

2. Provide complete stability data that includes the (b) (4) measurement to cover 0 weeks, 5 weeks, 10 weeks and 15 weeks time points for three batches of commercial scale drug product manufactured (b) (4) as part of the control strategy for homogeneity of the drug product. This stability data should also include testing that demonstrates that (b) (4) does not occur with the updated control strategy. The test for (b) (4) should be described and validated and included in the stability testing. As an alternative to this (b) (4) test, they could include testing on stability to verify that the problem of appropriate levels of levodopa and carbidopa in the morning dose is continuously solved throughout the term of stability testing.

Summary of the Applicant's Response to Deficiency #2:

- Eight weeks of the refrigerated stability testing data were provided with the resubmission, including the (b) (4) testing and the morning dose testing. This was from three commercial scale batches.
 - The remaining data to Fifteen weeks was submitted by amendment during the review cycle.
 - The morning dose method was used to simulate the first 30 minutes of the daily dosing period and to verify the appropriate levels of levodopa and carbidopa.
3. Submit the complete dissolution profile data (*individual, mean, SD, profiles*) for each time point for the dissolution testing of the commercial-scale batches. Provide the dissolution data at the following time points: 15, 20, 30, 40, 50, and 60 minutes (n=12). Report the dissolution data as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

Reviewer Comment: *This was required by the ONDQA biopharmaceutics reviewer Kelly Kitchens. For review details see the biopharmaceutics review.*

Summary of Applicant's Response to Deficiency #3:

- The first 8 weeks of data for the refrigerated stored commercial batches was provided with the resubmission.
 - The remaining data to 15 weeks was submitted by amendment during the review cycle.
4. We acknowledge your commitment to provide stability data for your drug product under frozen (-20°C) and refrigeration (5°C) conditions post-approval. However, for setting the specifications for your drug product, you will need to provide data from at least 3 batches at the initial time point and thereafter at 5, 10, and 15 weeks under refrigeration conditions. For this testing, we consider the initial time point to be when

the product is thawed and placed under the 5°C refrigeration conditions. For the dissolution testing, provide the complete dissolution profile data as described in the above comment.

Reviewer Comment: *This was required by the ONDQA biopharmaceutics reviewer Kelly Kitchens. For review details see the biopharmaceutics review.*

Summary of the Applicant's Response to Deficiency #4:

- The first 8 weeks of data for the refrigerated stored commercial batches was provided with the resubmission.
 - The remaining data to 15 weeks was submitted by amendment during the review cycle.
5. In your October 31, 2013 response to our Information Request (IR), you indicated that [REDACTED] (b) (4); whereas in your February 7, 2014 IR response, you indicated [REDACTED] (b) (4). Clarify this discrepancy [REDACTED] (b) (4).

Reviewer Comment: *This was required by the ONDQA biopharmaceutics reviewer Kelly Kitchens. For review details see the biopharmaceutics review.*

Summary of the Applicant's Response to Deficiency #5:

- i. The sponsor confirmed the correct value was [REDACTED] (b) (4) mg/mL/week.

Additional Comments (Product Quality)

- 1. Change all references from [REDACTED] (b) (4) to "carbidopa and levodopa enteral suspension" in the labeling to comply with Agency drug product dosage form naming conventions.

Summary of the Applicant's Response to Additional Comment #1:

They agreed to this.

- 2. The comparability protocol to accept [REDACTED] (b) (4) with a reporting category of annual report is not acceptable. This would require prior approval labeling changes.

Summary of the Applicant's Response to Additional Comment #2:

They indicated acceptance of this.

Product Quality Information Requests After the Resubmission

Submit the complete dissolution profile data (individual, mean, SD) for each time point for the dissolution testing of the following commercial-scale batches: Lot numbers 12D11G07, 12H09G07, 12J18G15, 13D11G13, 13D18G21, 13E10G08, 13F13G15, 13F20G23, 13H20G20, and 13J16G15.

Reviewer Comment: This was submitted by the biopharmaceutics reviewer. The requested data was received in eCTD 0034 on August 22, 2014. For further details, consult the biopharmaceutics review.

Product Quality Information Request sent October 9, 2014 (Mid-Cycle by Tracy Peters)

1. We agree with setting the expiration dating period for the refrigerated storage portion of drug product storage to 12 weeks (b) (4). We agree with your proposal to initiate Uniformity of Dispensed Cassette Contents (UDCC) as proposed for stability testing, except that we do not agree that a change to (b) (4) weeks expiration dating period for drug product stored at refrigerated conditions can be implemented with annual report notification to the Agency. This change results in a change in the label, thus requiring a pre-approval supplement. In this supplement you should provide the data resulting from stability studies done at (b) (4) weeks refrigerated storage on the first 10 commercial batches, the justification for increasing the expiration dating period to (b) (4) weeks, and an updated label. Your commitment to using the UDCC study on the annual stability batch after submission of the supplement to extend the expiration period is acceptable.

Summary of Applicant's Response (email response received 10/14/2014):

They acknowledged the change in expiration dating to 12 weeks for samples under refrigerated storage conditions, and that a change to (b) (4) weeks requires a pre-approval supplement. They will update their post-approval stability commitment with regard to the UDCC study.

2. The dose strength in the labeling (package insert and container labels) for Duopa of carbidopa monohydrate (b) (4) mg/mL is not acceptable because previously approved drug products report the carbidopa content on an anhydrous basis (i.e., the active moiety), which is consistent with current Agency and USP policies. Therefore, the drug product with respect to carbidopa should be labeled as 4.63 mg/mL, representing carbidopa on an anhydrous basis. For container labels the side bar should additionally indicate that the product contains carbidopa monohydrate at 5 mg/mL which is equivalent to 4.63 mg/mL of carbidopa.

Summary of Applicant's Response:

They agreed to describe the carbidopa content in the labeling as 4.63 mg/mL but propose to augment the labeling as follows:

Prescribing Information: (b) (4)

Cassette and carton labels: Each mL contains 5 mg carbidopa monohydrate (equivalent to 4.63 mg of carbidopa anhydrous) and 20 mg of levodopa.

3. To correct the label claim amount for carbidopa in the drug product specification, the following amendments and commitments are necessary:

- a. Assay limit of (b) (4) of label claim should be changed to carbidopa (b) (4) mg/mL. Other limits impacted by the label claim being associated with carbidopa versus carbidopa monohydrate should also be appropriately corrected.

Summary of Applicant's Response: They agree to this, and explicitly will change the limits of (b) (4) from (b) (4)% (based on monohydrate) to (b) (4)% (based on carbidopa anhydrous). (b) (4) will be changed from (b) (4)% to (b) (4)% respectively. Total degradation products will be changed from (b) (4)% to (b) (4)% respectively.

- b. The calculation and reporting sections of the methods RTM.C4812 (assay), RTM.C4812 (degradation products), RTM.C5531 (dissolution of carbidopa monohydrate), and RTM.C5607 (Uniformity of Dispensed Cassette Content for carbidopa monohydrate) should be modified to produce values for anhydrous carbidopa or relative to anhydrous carbidopa, rather than monohydrate. The methods do not need revalidation. To facilitate review of the revised methods, provide in your response, a table referencing the changed sections in the methods, with a side-by-side view of the original and modified sections so it is clear where the changes are made.

Summary of Applicants Response: Calculations in test methods RTM.C5531 (dissolution) will be revised as described. RTM.C5607 (uniformity of dispensed cassette contents) will only be updated to reference carbidopa as carbidopa anhydrous. In RTM.C4812 (Assay, Purity, ID) there will be references for both carbidopa monohydrate and anhydrous basis to satisfy multiple markets. Relative response factors will likewise be represented in both monohydrate and anhydrous basis. The justification of specifications will be updated to reflect these changes.

- c. You should commit to reporting all future data with regard to carbidopa monohydrate as carbidopa (anhydrous basis), using the appropriate adjustments in assay method calculations.

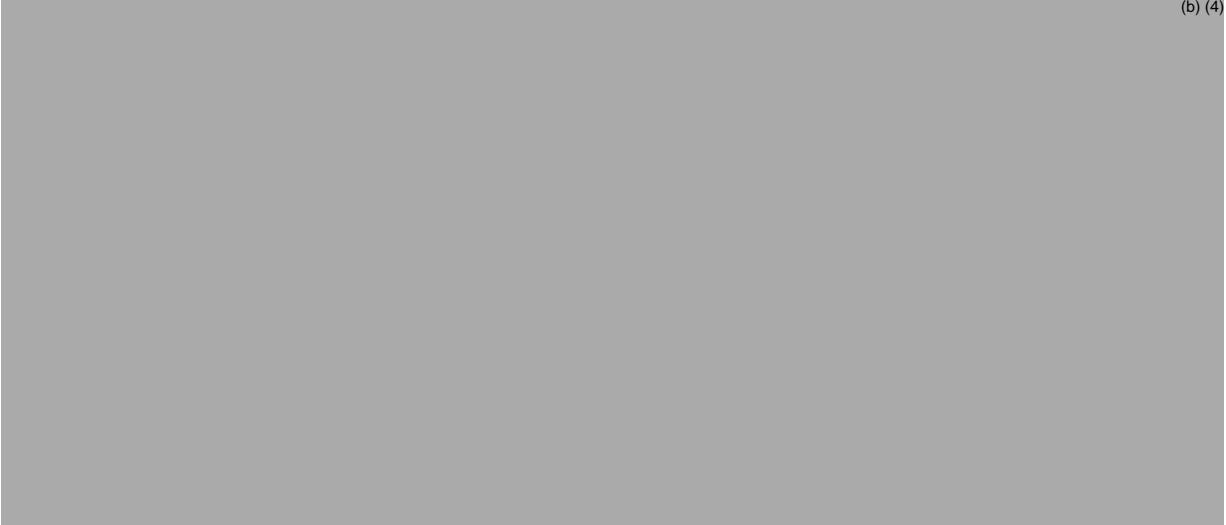
Summary of Applicant's Response: They commit to express all future carbidopa results in terms of the anhydrous basis. They understand they do not need to correct development documentation (e.g., certificates of analysis, analytical validation reports, completed stability studies, and process validation reports).

Product Quality Information Request sent October 20, 2014 (by Tracy Peters)

- ii. We recommend that prescribing information indicate the drug product strength as carbidopa 4.63 mg/mL and that the cassette and carton labels must indicate the same.

Summary of the Applicant's Response (part of amendment eCTD 0037 received 10/31/2014)

The applicant provided the following carton label which meeting these requirements:



The cassette label was also supplied and it meets the recommended criteria.

- iii. The augmented information (e.g., Each mL contains 5 mg carbidopa monohydrate (*equivalent to 4.63 mg of carbidopa anhydrous*) and 20 mg of levodopa) should also appear in the package insert, and on the cassette and carton labels in the usual places for explanatory information, however the drug product strength must indicate the concentration of carbidopa anhydrous (e.g., 4.63 mg/mL) and levodopa (e.g., 20 mg/mL) in the most prominent labeling position.

Summary of the Applicant's Response (part of amendment eCTD 0037 received 10/31/2014)

The applicant provided another round of draft labeling which did not meet this criteria. Further rounds of discussion are continuing.

Reviewer Comments: The negotiation process for final label wording often runs past the GRMP review deadline. This process is underway and will be pursued and completed if an overall approval recommendation is reached by the review team.

Amendment eCTD 0036 (9/11/2014) Provision of Full 15 Weeks Stability Data at Refrigerated Storage Conditions

- This included the full 15 weeks stability data from 3 commercial-scale lots, (b) (4) and morning dose testing.
- In addition, the applicant proposed a new control method, Uniformity of Dispensed Cassette Contents (UDCC) for monitoring product uniformity on stability. (b) (4)

The UDCC method is similar, except it measures the concentration of (b) (4) mL aliquots delivered from the cassette by the pump. It gives a measure of concentration uniformity across the whole cassette, (b) (4)

This considers the possibility that settling may occur on storage in parts of the cassette other than the region critical to delivering the first dose. The applicant agrees to make this a release specification and stability specification and test this for the first 10 commercial batches of drug product produced to demonstrate that (b) (4) is an adequate predictor of maintaining concentration uniformity for the drug product. Concentration uniformity is indicative homogeneity of the drug substance.

Reviewer Comments:

(b) (4)

the applicant will use 12 weeks as the expiration dating period for the refrigerated drug product life. This can be later changed if the stability data for the first 10 commercial lots demonstrates that concentration uniformity continues to be maintained above the specified limit. (b) (4)

Further testing will verify that the UDCC testing is an adequate predictor of homogeneity.

eCTD Sections

3.2.P.5.1 Specification for Levodopa - Carbidopa Enteral Suspension

Table 1. Specification for Levodopa-Carbidopa Intestinal Gel

Test	Analytical Procedure	Acceptance Criteria	Limit Type
Description	RTM.P1140	Off-white to slightly yellow homogeneous suspension	Shelf-life
Identification HPLC	RTM.C4812	The retention time of the peaks for Levodopa and Carbidopa in the product chromatogram should correspond to the peaks for the above mentioned substances in the calibration curve	Shelf-life
Identification TLC	RTM.I1567	The solution under test exhibits two spots with R _F values corresponding to those exhibited in the reference solutions	Shelf-life
Assay Levodopa	RTM.C4812	(b) (4) mg/mL (b) (4)% of label claim)	Shelf-life
Assay Carbidopa (anhydrous)	RTM.C4812	(b) (4) mg/mL (b) (4)% of label claim)	Shelf-life

Test	Analytical Procedure	Acceptance Criteria	Limit Type
Degradation Products Specified Degradation Products	RTM.C4812	(b) (4)	Shelf-life
		NMT (b) (4)% as carbidopa, anhydrous	Shelf-life
Degradation Products Unspecified Degradation Product	RTM.C4812	(b) (4)	Shelf-life
		NMT (b) (4)% as carbidopa, anhydrous	Shelf-life
		NMT (b) (4)% of carbidopa, anhydrous	Shelf-life
Hydrazine	RTM.C4813	NMT (b) (4) µg/g gel	Shelf-life
Viscosity (b) (4)	RTM.P1094	(b) (4)	Shelf-life
Viscosity (b) (4)	RTM.P1182	NLT (b) (4)	Shelf-life
pH	USP <791>	(b) (4)	Shelf-life
Microbiological			Shelf-life
Total Aerobic Microbial Count	USP <61>	NMT (b) (4) cfu/g	
Total Yeast and Molds	USP <61>	NMT (b) (4) cfu/g	
E. coli	USP <62>	(b) (4)/g	
Dissolution, levodopa	RTM.C5531	(b) (4) Q = (b) (4) in 40 minutes	Shelf Life
Dissolution, carbidopa (anhydrous)	RTM.C5531	(b) (4) Q = (b) (4) in 40 minutes	Shelf Life

Test	Analytical Procedure	Acceptance Criteria	Limit Type
Uniformity of Dispensed Cassette Content: Levodopa (for stability only, not tested for lot release)	RTM.C5607	Meets USP <905> L1 = (b) (4) L2 = (b) (4) Meets USP <905> criterion for deviation of each result from M at both N=10 and N=30	Shelf Life
Uniformity of Dispensed Cassette Content: Carbidopa Monohydrate (for stability only, not tested for lot release)	RTM.C5607	Meets USP <905> L1 = (b) (4) L2 = (b) (4) Meets USP <905> criterion for deviation of each result from M at both N=10 and N=30	Shelf Life

NMT = not more than
R_F = retention factor

Reviewer Comments: For this cycle of review, the specification attributes needing further justification are:

- *The Dissolution Specification (being reviewed by Kelly Kitchens - ONDQA Biopharmaceutics Reviewer)*



- *The uniformity of dispensed cassette contents (UDCC) specification.*
 - *This is the proposal by the applicant to establish a standard test for overall uniformity.*



This is the reason for the commitment by the sponsor to test the first 10 commercial lots using the new specification (UDCC). The

applicant agrees to accept 12 weeks expiration dating period

(b) (4)

In this 10 batch testing, the UDCC study will by default include 3 cassettes being tested per batch. If stability is verified, the UDCC study will revert to 1 cassette being tested for the annual stability batch, with level 2 testing only taking place if required by results of the level 1 testing.

3.2.P.8.1 Stability Summary and Conclusions for Levodopa-Carbidopa Enteral Suspension

This includes data from the 15-week study on 3 commercial-scale lots of drug product. These three lots were manufactured at the (b) (4) manufacturing facility, which is the commercial manufacturing site. The product cassette reservoirs were packaged into corrugated cardboard boxes (7 per secondary package). In addition to the 15 week study data (implemented in 2014), supplemental studies were done to include:

- a photostability study
- temperature cycling studies to support the dual frozen and refrigerated storage
- an extended study at the accelerated condition 25°C/60%RH

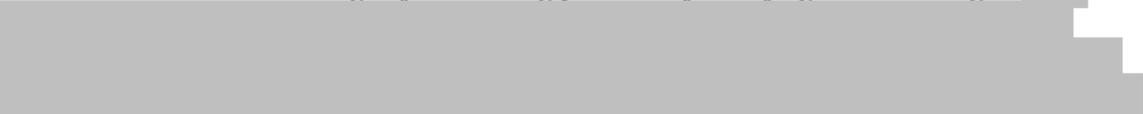
The supplemental studies were covered in the original review.

Manufacturing data for the three primary stability batches for this resubmission are captured here:

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page



Reviewer Comments: The applicant's updated stability data on 3 commercial batches of drug product, evaluated over 15 weeks, at refrigerated storage leads them to recommend 12 weeks storage of their drug product after refrigerated storage. (b) (4)



This proposal is accepted. It is also recommended to concur with the applicant's request to assign expiration dating for 12 weeks of refrigerated storage. This allows up to 24 months of freezer storage before thawing to store in the refrigerator. Cassettes should be used on the same day they are removed from the refrigerator or discarded. They can be used as soon as they reach room temperature.

Charles Jewell -S

Digitally signed by Charles Jewell -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Charles Jewell -S,
0.9.2342.19200300.100.1.1=2000403529
Date: 2014.11.10 14:09:55 -05'00'

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen
Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2014.11.10 14:41:38 -05'00'

NDA 203952

**Duopa
(Levodopa-Carbidopa) enteral suspension**

Abbvie, Inc.

**Charles F. Jewell Jr.
Division of Neurology Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	12
III. Administrative.....	12
A. Reviewer's Signature.....	12
B. Endorsement Block.....	12
C. CC Block	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	19
S DRUG SUBSTANCE [Carbidopa Monohydrate, (b) (4)].....	19
S DRUG SUBSTANCE [Levodopa, (b) (4)].....	19
P DRUG PRODUCT [Levodopa-Carbidopa Intestinal Gel (LCIG), intestinal gel ***].....	20
A APPENDICES	21
R REGIONAL INFORMATION	21
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	21
A. Labeling & Package Insert	21
B. Environmental Assessment Or Claim Of Categorical Exclusion	21
III. List Of Deficiencies To Be Communicated (This includes a copy of the comments from Kelly Kitchens' ONDQA Biopharmaceutical review for convenience in viewing).....	21

APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 203952
2. REVIEW # 2:
3. REVIEW DATE: 07-Mar-2014
4. REVIEWER: Charles F. Jewell Jr.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
SDN 1 - New NDA	16-NOV-2012
Filing Review/Initial Quality Assessment -Charles Jewell	21-DEC-2012
Refuse to File – Stacy M. Metz	15-JAN-2013
SDN 11 - Meeting Request	16-JAN-2013
Meeting Request Granted - Stacy M. Metz	23-JAN-2013
Meeting Minutes - Stacy M. Metz	11-APR-2013
Intercenter/Combination Products Consult - Stacy M. Metz to Jacqueline Ryan / Alan Stevens (CDRH)	04-JUN-2013
Intercenter/Combination Products Consult - Stacy M. Metz to Ron Kaye and Quynh Nhu Nguyen (CDRH Human Factors)	04-JUN-2013
Intercenter/Combination Products Consult - Stacy M. Metz to Carl Fischer (CDRH Office of Compliance)	04-JUN-2013
Filing Review after RTF - Charles Jewell	01-JUL-2013
Intercenter/Combination Products Consult - Teshara G. Bouie to Jeffrey Cooper (Hospital Devices)	02-JUL-2013

Chemistry Review Data Sheet

Quality Micro Final Review by Vinayak Pawar	01-Aug-2013
Information Request - Teshara Bouie to Applicant, regarding dissolution method needing to be more suitable to simulate physiological conditions. Based on deficiencies cited by ONDQA Biopharmaceutics reviewer Kelly Kitchens.	31-Oct-2013
CMC Review #1 by Charles Jewell	28-Jan-2014
Quality Biopharmaceutical Review by Kelly Kitchens	21-Feb-2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SDN 1 - New NDA	16-NOV-2012
SDN 16 - Resubmission after Refuse to File	28-MAY-2013
SDN 22 - Quality Information Response to IR, CDRH related information.	26-AUG-2013
SDN 23 - Multiple Categories (Response to Biopharmaceutics IR on Dissolution)	18-SEP-2013
SDN 27 - Multiple Categories but include responses to IR from Kelly Kitchens, Biopharmaceutics Reviewer (Improved dissolution method)	19-DEC-2013
SDN 30 - Quality Responses	10-FEB-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	AbbVie Inc.
Address:	1 N. Waukegan Road Dept. PA77/Bldg. AP30 North Chicago, IL 60064
Representative:	Matthew Kuntz, PharmD, MBA, RAC, Director, Regulatory Affairs
Telephone:	847-938-0009

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Duopa
- b) Non-Proprietary Name (USAN): levodopa-carbidopa intestinal gel
- c) Code Name/# (ONDC only): LCIG

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Anti-Parkinson Drug Combination

11. DOSAGE FORM: Enteral Suspension

12. STRENGTH/POTENCY: 20 mg/mL (Levodopa), 5 mg/mL (Carbidopa)

13. ROUTE OF ADMINISTRATION: Enteral via PEG-J

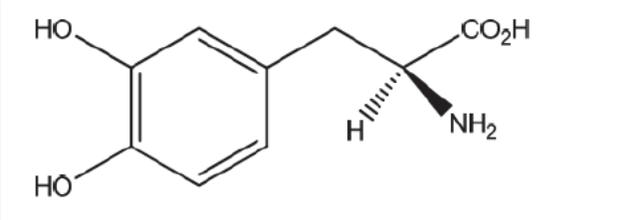
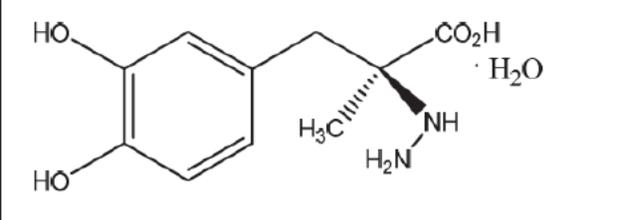
14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

	
Levodopa (S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid C ₉ H ₁₁ NO ₄	Carbidopa Monohydrate (S)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid C ₁₀ H ₁₄ N ₂ O ₄ · H ₂ O

Chemistry Review Data Sheet

MW: 197.19	MW: 244.24 (as monhydrate)
------------	----------------------------

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			(b) (4)	4	Adequate	Outstanding stability amendment 1/05/2014 in response to IR	LOA 19-APR-2013
				4	Adequate	Outstanding stability amendment/Ann . Rpt. 3/9/2013	LOA 19-APR-2013
				4	Adequate	Sufficient Info in Application	LOA 17-APR-2013
	Device Master File					Under Review by CDRH	LOA 17-APR-2013

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60663	IND for LCIG by applicant

18. STATUS:

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Overall Acceptable	3/7/2014	Office of Compliance
Pharm/Tox	CR	2/21/2014	LuAnn McKinney
Biopharm	CR	2/21/2014	Kelly Kitchens
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	Adequate	1/27/2014	Charles Jewell
Microbiology	Approval	7/31/2013	Vinayak B. Pawar, Ph.D.

The Chemistry Review for NDA 203952

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

A complete response is recommended for this application from the CMC perspective based on the deficiencies outlined below. The CDER Office of Compliance has issued an overall acceptable rating for the manufacturing sites as described in the attached EES report dated 7-Mar-2014.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This drug product is an enteral suspension of levodopa and carbidopa monohydrate particles in a solution of carmellose sodium in purified water. (b) (4)

The suspension is packaged in plastic (b) (4) bag inside a hard plastic (b) (4) container (cassette). This cassette contains approximately 100 g of suspension. The concentration of levodopa is 20 mg/mL, for carbidopa monohydrate 5 mg/mL and for carmellose sodium (b) (4) mg/mL. One cassette contains a total of 2000 mg of levodopa, 500 mg of carbidopa monohydrate and (b) (4) mg of carmellose sodium. The cassette is designed for use in an administration system which involves an infusion pump that connects to either naso-jejunal (NJ) tubing or percutaneous endoscopic gastrostomy (PEG) tubing which is connected to jejunal (J) tubing. The pump is designed to work with the cassette to deliver a continuous infusion of the enteral suspension directly to the jejunum.

The pump is programmed to deliver a morning dose (bolus rate higher than the normal infusion rate), the continuous infusion and extra doses (short bursts at a higher than normal infusion rate). The pump has three lock levels for programming. Level 0 and level 1 require passcodes and are designed for original set-up by the physician and for the main health care provider. Level 2 is set for use by the patient, with limited controls. Level 2 allows only stopping and starting the pump, reset of the reservoir volume, starting an extra dose and starting the morning dose. Level 2 does not allow any programming. The morning dose and extra dose mode accelerates the pumping over the continuous rate during the bolus periods. There is one morning dose and a number of extra doses may be allowed, as determined by the physician level programmer. The maximum possible continuous rate is 20 mL/hr. This rate can be varied in level 1. Maximum accessible rate can be programmed in level 0. Continuous dosing can vary from 0.0 mL/hr to 20.0 mL/hr in

Executive Summary Section

0.1 mL/hr increments. The morning dose can be set in 0.1 mL increments to a maximum of 20 mL. The extra dose can be set in 0.1 mL increments to a maximum of 9.9 mL. The rate for an extra dose or morning dose can be as high as 40 mL/hr, the continuous rate plus the fastest rate to achieve the bolus dose. The pump can operate at 125 mL/hr in priming mode.

The control for number of morning doses or extra doses is achieved by locking out a new dose for a set period of time. The morning dose lockout is from 1 to 24 hours in 1 hour increments. The extra dose lockout is from 15 minutes to 24 hours in 15 minute increments.

The drug substances are levodopa and carbidopa monohydrate, both are manufactured for the proposed commercial product by (b) (4) and are fully described in DMFs. Both of these drug substances from this manufacturer are approved for use by the Agency in other drug products.

The pump is described completely in a MAF filed with CDRH, and CDRH was consulted by OND to review the MAF with respect to this combination product.

The container closure system, the (b) (4) cassette, is described in a DMF, but is also adequately described in this application.

The tubing sets (NJ and PEG-J and connecting tubing) recommended by the applicant for use with this product either already have received marketing clearance from CDRH (as feeding tubes) or they are in the process of receiving marketing clearance from CDRH (specially designed tubing sets proposed for marketing by the applicant, based on already cleared feeding tubes). These reviews have been consulted to CDRH.

The proposed combination device is relatively complex to operate and care for. Because of this, both CDER's and CDRH's Human Factors Evaluation reviewers are involved with assessing the safe and effective usability of this combination of drug product and devices (drug product cassette, infusion pump, connector tubing, NJ and PEG-J tubing sets). Safety and efficacy of the use of levodopa and carbidopa for Parkinson's patients is well understood. The greatest safety concerns for this product are due to complications in using the pump and tubing (pump failures, tubing clogging, improperly positioned internal tubing etc.), thus the need for careful Human Factors evaluation.

This drug product is a stabilized, homogeneous suspension of (b) (4) levodopa and carbidopa monohydrate, which represents a novel formulation for these drugs. Carbidopa (b) (4) in this formulation compared with solid-oral-dosage forms. The key degradation products are hydrazine, (b) (4) and (b) (4). The proposed specified limits for these degradation products are at unprecedented levels. The applicant has attempted to justify these levels in light of the benefit/risk of using this drug in advanced Parkinson's patients. The acceptance of this justification is being determined by the non-clinical reviewers of this application.

Executive Summary Section

While all of the above considerations are interdisciplinary in nature, there are two important deficiencies continuing to be resolved by the applicant which relate directly to chemistry, manufacturing and controls for the drug product. These involve the controls for homogeneity of the drug product and the physiologically relevant quality control dissolution method for this novel product. The Agency CMC reviewers and biopharmaceutical reviewers have been communicating regularly with the applicant with regard to these issues. At this time, the applicant has proposed a reasonable hypothesis for homogeneity issues seen with their product and proposed a logical control strategy for addressing the issue. However, the data necessary to support the hypothesis and proposed control strategy have not been submitted to the NDA. These major amendments might be sufficient to support an "approval" recommendation from CMC, but will not be reviewed in this cycle unless the review clock is extended.

The homogeneity issues involve examples of (b) (4) which have been shown to lower the exposure of levodopa during the morning dose. Prior to communication of this problem, the applicant had indicated that problems with (b) (4) were completely controlled by (b) (4)

Based on further study, the applicant now recommends (b) (4)

Although the logic and preliminary data of this change has been discussed with the agency, we are awaiting the confirmatory data to support this finding. Homogeneity needs to be maintained for up to 24 months of frozen storage, followed by up to (b) (4) weeks of refrigerated storage, and up to 24 hours at room temperature to support the proposed use of the product.

For the dissolution method, the sponsor needs to demonstrate a method that supports adequate dissolution at conditions that adequately represent the introduction of the drug product suspension directly into the jejunum at a relatively slow steady rate, (b) (4)

B. Description of How the Drug Product is Intended to be Used

Based on the description of the drug product/device combination product discussed above, the following description of intended use is given:

For advanced Parkinson's patients, that are experiencing a high degree of off-time with current standard therapy (mostly oral levodopa/carbidopa) it is proposed that these agents introduced in a continuous fashion, directly to the jejunum, by-passing delays due to interference with uptake due to stomach residence time, will reduce off-time.

This can be accomplished by by-passing the stomach with either a nasal feeding tube with jejunal extension (NJ) or a percutaneous endoscopic gastrostomy tube with jejunal extension (PEG-J). The nasal tube strategy is recommended to try to evaluate potential effectiveness and if it is effective, subject the patient to endoscopic insertion of the PEG-J tube. (b) (4)

Executive Summary Section

(b) (4)

It is envisioned that continuous delivery will occur for 16 hours a day, starting with an initial bolus dose in the morning (morning dose) and with the option for extra doses during the day when the patient feels off-time coming on. It is also envisioned that most patients can experience improved on-time / off-time ratio with the use of one (b) (4) cassettes of drug product per day. (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

Based on deficiencies in drug product homogeneity control and dissolution control, this application is not recommended for approval. In addition, the non-clinical reviewer LuAnn McKinney maintains that unprecedented levels of impurities exist (Hydrazine, (b) (4) and (b) (4)) and the requirements for qualification are discussed in her review. The Office of Compliance has issued an overall acceptable recommendation for the manufacturing sites involved in this application through the Establishment Evaluation System.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

10 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLES F JEWELL
03/07/2014

OLEN M STEPHENS
03/07/2014

NDA 203952

**Duopa
(Levodopa-Carbidopa) enteral suspension**

Abbvie, Inc.

**Charles F. Jewell Jr.
Division of Neurology Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	12
III. Administrative.....	12
A. Reviewer's Signature.....	12
B. Endorsement Block.....	12
C. CC Block	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	13
S DRUG SUBSTANCE [Carbidopa Monohydrate, (b) (4)].....	13
S DRUG SUBSTANCE [Levodopa, (b) (4)].....	20
P DRUG PRODUCT [Levodopa-Carbidopa Intestinal Gel (LCIG), intestinal gel ***].....	28
A APPENDICES	80
R REGIONAL INFORMATION	80
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	80
A. Labeling & Package Insert	81
B. Environmental Assessment Or Claim Of Categorical Exclusion	81
III. List Of Deficiencies To Be Communicated.....	81

APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 203952
2. REVIEW # 1:
3. REVIEW DATE: 28-Jan-2014
4. REVIEWER: Charles F. Jewell Jr.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
SDN 1 - New NDA	16-NOV-2012
Filing Review/Initial Quality Assessment -Charles Jewell	21-DEC-2012
Refuse to File – Stacy M. Metz	15-JAN-2013
SDN 11 - Meeting Request	16-JAN-2013
Meeting Request Granted - Stacy M. Metz	23-JAN-2013
Meeting Minutes - Stacy M. Metz	11-APR-2013
Intercenter/Combination Products Consult - Stacy M. Metz to Jacqueline Ryan / Alan Stevens (CDRH)	04-JUN-2013
Intercenter/Combination Products Consult - Stacy M. Metz to Ron Kaye and Quynh Nhu Nguyen (CDRH Human Factors)	04-JUN-2013
Intercenter/Combination Products Consult - Stacy M. Metz to Carl Fischer (CDRH Office of Compliance)	04-JUN-2013
Filing Review after RTF - Charles Jewell	01-JUL-2013
Intercenter/Combination Products Consult - Teshara G. Bouie to Jeffrey Cooper (Hospital Devices)	02-JUL-2013

Chemistry Review Data Sheet

Information Request - Teshara Bouie to Applicant, 31-Oct-2013
regarding dissolution method needing to be more
suitable to simulate physiological conditions.
Based on deficiencies cited by ONDQA
Biopharmaceutics reviewer Kelly Kitchens.

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SDN 1 - New NDA	16-NOV-2012
SDN 16 - Resubmission after Refuse to File	28-MAY-2013
SDN 22 - Quality Information Response to IR, CDRH related information.	26-AUG-2013
SDN 23 - Multiple Categories (Response to Biopharmaceutics IR on Dissolution)	18-SEP-2013
SDN 27 - Multiple Categories but include responses to IR from Kelly Kitchens, Biopharmaceutics Reviewer (Improved dissolution method)	19-DEC-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	AbbVie Inc.
Address:	1 N. Waukegan Road Dept. PA77/Bldg. AP30 North Chicago, IL 60064
Representative:	Matthew Kuntz, PharmD, MBA, RAC, Director, Regulatory Affairs
Telephone:	847-938-0009

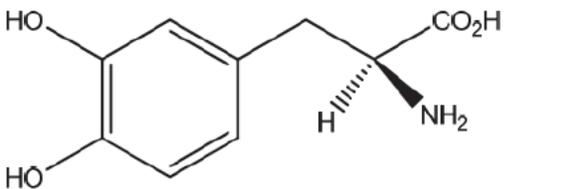
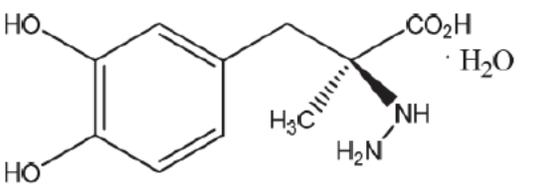
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Duopa
- b) Non-Proprietary Name (USAN): levodopa-carbidopa intestinal gel
- c) Code Name/# (ONDC only): LCIG
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Anti-Parkinson Drug Combination
11. DOSAGE FORM: Enteral Suspension
12. STRENGTH/POTENCY: 20 mg/mL (Levodopa), 5 mg/mL (Carbidopa)
13. ROUTE OF ADMINISTRATION: Enteral via PEG-J
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

	
<p style="text-align: center;">Levodopa</p> <p>(S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid $C_9H_{11}NO_4$ MW: 197.19</p>	<p style="text-align: center;">Carbidopa Monohydrate</p> <p>(S)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid $C_{10}H_{14}N_2O_4 \cdot H_2O$ MW: 244.24 (as monhydrate)</p>

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			(b) (4)	4	Adequate	Outstanding stability amendment 1/05/2014 in response to IR	LOA 19-APR-2013
				4	Adequate	Outstanding stability amendment/Ann . Rpt. 3/9/2013	LOA 19-APR-2013
				4	Adequate	Sufficient Info in Application	LOA 17-APR-2013
	Device Master File					Under Review by CDRH	LOA 17-APR-2013

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60663	IND for LCIG by applicant

18. STATUS:

ONDC:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		Office of Compliance
Pharm/Tox	Pending		LuAnn McKinney
Biopharm	Pending		Kelly Kitchens
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	Adequate	1/27/2014	Charles Jewell
Microbiology	Approval	7/31/2013	Vinayak B. Pawar, Ph.D.

The Chemistry Review for NDA 203952

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

A complete response is recommended for this application from the CMC perspective pending resolution of drug product homogeneity issues and recommendations from OC, the non-clinical reviewer, and biopharmaceutics. As of the date of this review, it is still possible that the applicant may resolve the CMC deficiencies by amendments that are expected. See deficiencies outlined in the summaries below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This drug product is an enteral suspension of levodopa and carbidopa monohydrate particles in a solution of carmellose sodium in purified water. (b) (4)

The suspension is packaged in plastic (b) (4) bag inside a hard plastic (b) (4) container (cassette). This cassette contains approximately 100 g of suspension. The concentration of levodopa is 20 mg/mL, for carbidopa monohydrate 5 mg/mL and for carmellose sodium (b) (4) mg/mL. One cassette contains a total of 2000 mg of levodopa, 500 mg of carbidopa monohydrate and (b) (4) mg of carmellose sodium. The cassette is designed for use in an administration system which involves an infusion pump that connects to either naso-jejunal (NJ) tubing or percutaneous endoscopic gastrostomy (PEG) tubing which is connected to jejunal (J) tubing. The pump is designed to work with the cassette to deliver a continuous infusion of the enteral suspension directly to the jejunum.

The pump is programmed to deliver a morning dose (bolus rate higher than the normal infusion rate), the continuous infusion and extra doses (short bursts at a higher than normal infusion rate). The pump has three lock levels for programming. Level 0 and level 1 require passcodes and are designed for original set-up by the physician and for the main health care provider. Level 2 is set for use by the patient, with limited controls. Level 2 allows only stopping and starting the pump, reset of the reservoir volume, starting an extra dose and starting the morning dose. Level 2 does not allow any programming. The morning dose and extra dose mode accelerates the pumping over the continuous rate during the bolus periods. There is one morning dose and a number of extra doses may be allowed, as determined by the physician level programmer. The maximum possible continuous rate is 20 mL/hr. This rate can be varied in level 1. Maximum accessible

Executive Summary Section

rate can be programmed in level 0. Continuous dosing can vary from 0.0 mL/hr to 20.0 mL/hr in 0.1 mL/hr increments. The morning dose can be set in 0.1 mL increments to a maximum of 20 mL. The extra dose can be set in 0.1 mL increments to a maximum of 9.9 mL. The rate for an extra dose or morning dose can be as high as 40 mL/hr, the continuous rate plus the fastest rate to achieve the bolus dose. The pump can operate at 125 mL/hr in priming mode.

The control for number of morning doses or extra doses is achieved by locking out a new dose for a set period of time. The morning dose lockout is from 1 to 24 hours in 1 hour increments. The extra dose lockout is from 15 minutes to 24 hours in 15 minute increments.

The drug substances are levodopa and carbidopa monohydrate, both are manufactured for the proposed commercial product by (b) (4) and are fully described in DMFs. Both of these drug substances from this manufacturer are approved for use by the Agency in other drug products.

The pump is described completely in a MAF filed with CDRH, and CDRH was consulted by OND to review the MAF with respect to this combination product.

The container closure system, the (b) (4) cassette, is described in a DMF, but is also adequately described in this application.

The tubing sets (NJ and PEG-J and connecting tubing) recommended by the applicant for use with this product either already have received marketing clearance from CDRH (as feeding tubes) or they are in the process of receiving marketing clearance from CDRH (specially designed tubing sets proposed for marketing by the applicant, based on already cleared feeding tubes). These reviews have been consulted to CDRH.

The proposed combination device is relatively complex to operate and care for. Because of this, both CDER's and CDRH's Human Factors Evaluation reviewers are involved with assessing the safe and effective usability of this combination of drug product and devices (drug product cassette, infusion pump, connector tubing, NJ and PEG-J tubing sets). Safety and efficacy of the use of levodopa and carbidopa for Parkinson's patients is well understood. The greatest safety concerns for this product are due to complications in using the pump and tubing (pump failures, tubing clogging, improperly positioned internal tubing etc.), thus the need for careful Human Factors evaluation.

This drug product is a stabilized, homogeneous suspension of (b) (4) levodopa and carbidopa monohydrate, which represents a novel formulation for these drugs. Carbidopa (b) (4) in this formulation compared with solid-oral-dosage forms. The key degradation products are hydrazine, (b) (4) and (b) (4). The proposed specified limits for these degradation products are at unprecedented levels. The applicant has attempted to justify these levels in light of the benefit/risk of using this drug in advanced Parkinson's patients. The acceptance of this justification is being determined by the non-clinical reviewers of this application.

Executive Summary Section

While all of the above considerations are interdisciplinary in nature, there are two important deficiencies continuing to be resolved by the applicant which relate directly to chemistry, manufacturing and controls for the drug product. These involve the controls for homogeneity of the drug product and the physiologically relevant quality control dissolution method for this novel product. The Agency CMC reviewers and biopharmaceutical reviewers have been communicating regularly with the applicant with regard to these issues. At this time, the applicant has proposed a reasonable hypothesis for homogeneity issues seen with their product and proposed a logical control strategy for addressing the issue. However, the data necessary to support the hypothesis and proposed control strategy have not been submitted to the NDA. These major amendments might be sufficient to support an "approval" recommendation from CMC, but will not be reviewed in this cycle unless the review clock is extended.

The homogeneity issues involve examples of (b) (4) which have been shown to lower the exposure of levodopa during the morning dose. Prior to communication of this problem, the applicant had indicated that problems with (b) (4) were completely controlled by (b) (4)

Based on further study, the applicant now recommends using a (b) (4)

Although the logic and preliminary data of this change has been discussed with the agency, we are awaiting the confirmatory data to support this finding. Homogeneity needs to be maintained for up to 24 months of frozen storage, followed by up to (b) (4) weeks of refrigerated storage, and up to 24 hours at room temperature to support the proposed use of the product.

For the dissolution method, the sponsor needs to demonstrate a method that supports adequate dissolution at conditions that adequately represent the introduction of the drug product suspension directly into the jejunum at a relatively slow steady rate, (b) (4)

B. Description of How the Drug Product is Intended to be Used

Based on the description of the drug product/device combination product discussed above, the following description of intended use is given:

For advanced Parkinson's patients, that are experiencing a high degree of off-time with current standard therapy (mostly oral levodopa/carbidopa) it is proposed that these agents introduced in a continuous fashion, directly to the jejunum, by-passing delays due to interference with uptake due to stomach residence time, will reduce off-time.

This can be accomplished by by-passing the stomach with either a nasal feeding tube with jejunal extension (NJ) or a percutaneous endoscopic gastrostomy tube with jejunal extension (PEG-J). The nasal tube strategy is recommended to try to evaluate potential effectiveness and if it is effective, subject the patient to endoscopic insertion of the PEG-J tube (b) (4)

Executive Summary Section

(b) (4)

It is envisioned that continuous delivery will occur for 16 hours a day, starting with an initial bolus dose in the morning (morning dose) and with the option for extra doses during the day when the patient feels off-time coming on. It is also envisioned that most patients can experience improved on-time / off-time ratio with the use of one (b) (4) cassettes of drug product per day. (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

Based on deficiencies in drug product homogeneity control and dissolution method, this application is not recommended for approval. In addition, the non-clinical reviewer LuAnn McKinney maintains the unprecedented levels of (b) (4) and (b) (4) has not been adequately qualified for approval of this application. From a chemistry perspective it is not likely that these levels can be controlled using additional quality and manufacturing measures, since they appear to be a natural result of the formulation. The Office of Compliance has not yet issued an overall acceptable recommendation for the manufacturing sites involved in this application through the Establishment Evaluation System. There are pending issues with regard to human factors studies for the drug product administration system. These studies appear incomplete and more studies will be required.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

70 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLES F JEWELL
01/28/2014

OLEN M STEPHENS
01/28/2014

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 203952/000
Comp Date: 16-NOV-2012
Regulatory: 28-MAR-2014

Action Goal:
District Goal: 27-JAN-2014

Applicant: ABBVIE
 1 NORTH WAUKEGAN RD DEPT PA77/BLDG AF
 NORTH CHICAGO, IL 60064

Brand Name: LEVODOPA-CARBIDOPA INTESTINAL GEL
Estab. Name:
Generic Name: LEVODOPA-CARBIDOPA INTESTINAL GEL

Priority: 3
Org. Code: 120

Product Number; Dosage Form; Ingredient; Strengths
 001; GEL; LEVODOPA; 20MG
 001; GEL; CARBIDOPA; 5MG

Application Comment:

FDA Contacts:	C. JEWELL	Prod Qual Reviewer	3017964232
	T. BOUIE	Product Quality PM	3017961649
	S. METZ	Regulatory Project Mgr (HFD-120)	3017962139
	M. HEIMANN	Team Leader	3017961678

Overall Recommendation:	ACCEPTABLE	on 07-MAR-2014	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 27-AUG-2013	by EES_PROD		
	PENDING	on 20-AUG-2013	by EES_PROD		
	PENDING	on 19-JUN-2013	by EES_PROD		
	PENDING	on 03-DEC-2012	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: (b) (4). (on 19-JUN-2013 by T. BOUIE () 3017961649)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	19-JUN-2013				BOUIET
OC RECOMMENDATION (b) (4) INSPECTION PER FACTS: "LABORATORIES FOR BOTH ANALYTICAL AND MICROBIOLOGICAL CONTROL AND MONITORING WAS REVIEWED IN DEPTH WHICH WAS NOT COVERED IN DEPTH ON THE (b) (4) INSPECTION"	20-JUN-2013			ACCEPTABLE BASED ON PROFILE	CAPACCIDANIC

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
(b) (4)

Establishment Comment: (b) (4)

DRUG SUBSTANCE MANUFACTURING AND TESTING. (on 29-NOV-2012 by T. BOUIE (13017961649))

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-DEC-2012				BOUIET
OC RECOMMENDATION	17-DEC-2012			ACCEPTABLE BASED ON PROFILE	SMITHDE
REQUEST CANCELLED	15-JAN-2013			REFUSE TO FILE	EES_ADMIN
SUBMITTED TO OC	19-JUN-2013				BOUIET
OC RECOMMENDATION	20-JUN-2013			ACCEPTABLE BASED ON PROFILE	CAPACCIDANIC

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)



DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DRUG PRODUCT MANUFACTURING, PACKAGING, TESTING (on 29-NOV-2012 by T. BOUIE () 3017961649)

Profile: SUSPENSIONS AND EMULSIONS (NON PARENTERALS) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-DEC-2012				BOUIET
SUBMITTED TO DO	07-DEC-2012	Product Specific and GMP Inspection			SHARPT
ASSIGNED INSPECTION TO IB	28-DEC-2012	Product Specific and GMP Inspection			BRYKMANR
REQUEST CANCELLED	15-JAN-2013			REFUSE TO FILE	EES_ADMIN
SUBMITTED TO OC	19-JUN-2013				BOUIET
SUBMITTED TO DO	20-JUN-2013	Product Specific and GMP Inspection			CAPACCIDANIC
NEW DOSAGE FORM FOR ESTABLISHMENT					
ASSIGNED INSPECTION TO IB	24-JUN-2013	Product Specific and GMP Inspection			PHILPYE
INSPECTION SCHEDULED	25-OCT-2013		13-DEC-2013		BSEEMAN
INSPECTION PERFORMED	20-DEC-2013		20-DEC-2013		Robert.Steyert
AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED Please refer to TURBO EIR.					
DO RECOMMENDATION	06-MAR-2014			ACCEPTABLE BASED ON FILE REVIEW	MROSE
OC RECOMMENDATION DISTRICT RECOMMENDATION	07-MAR-2014			ACCEPTABLE DISTRICT RECOMMENDATION	CAPACCIDANIC

